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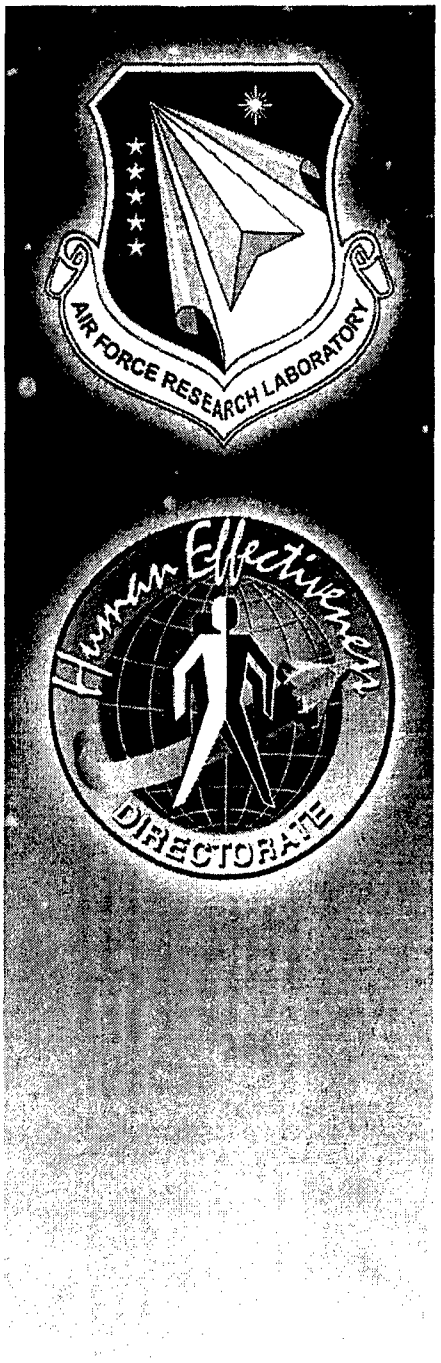

Air Force Research Laboratory

AN ASSESSMENT OF MODAFINIL FOR VESTIBULAR AND AVIATION-RELATED EFFECTS

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14. ABSTRACT
The goal of this study was to provide data concerning both the efficacy and the safe-to-fly dosage of a relatively unique compound, modafinil. Previous studies have indicated that modafinil holds promise as an effective wake-promoting agent for military personnel assigned to sustained operations without the common side effects associated with amphetamine-like substances. The present research was conducted to examine whether 200 or 400 mg doses of modafinil have any effect upon human vestibular functioning at night, to verify its cognitive enhancement capabilities during a short-term, sleep-loss setting, and to document the presence/absence of subjective symptoms. Other measures were investigated for possible effects of over-confidence or dehydration.

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PREFACE

This report covers the project period of 1 July 1999 to 15 December 2001. The work was performed under Job Order Number 71845901. Most of the work was performed by the following three contractors:

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SUMMARY

The goal of this study was to provide data concerning both the efficacy and the safe-to-fly dosage of a relatively unique compound, modafinil. This medication had been studied since 1986. The research has indicated that modafinil holds promise as an effective wake-promoting agent for military personnel assigned to sustained operations without the common side effects associated with amphetamine-like substances. The present research was conducted to examine whether 200 or 400 mg doses of modafinil have any effect upon human vestibular functioning at night, to verify its cognitive enhancement capabilities during a short-term, sleep-loss setting, and to document the presence/absence of drug related symptoms. Other measures were investigated for possible effects of overconfidence or dehydration.

Methods: Seventeen participants completed the double-blind repeated measures study. Each participant received three modafinil doses: 400 mg, 200 mg, and 0 mg (placebo), taken at 11:30 p.m. during separate, 12-hour overnight, sleep-loss sessions. Dose order was counterbalanced and the sessions were separated from each other by at least six days. Vestibular, cognitive, physiological and subjective symptom data were collected throughout the experimental sessions.

Results: Of the 13 vestibular outcome measures studied, only six were found to be sensitive (i.e., showed significant changes over time during the placebo session) to the effects of fatigue/circadian rhythm. For two of these (the saccadic and gain components of smooth pursuit visual tracking), modafinil was found to significantly protect against degradation during fatigue, as compared to the placebo condition. There were no vestibular outcome measures for which modafinil showed more degradation than placebo. Modafinil significantly eliminated or reduced early-morning performance decrements in all four cognitive and vigilance tasks showing the expected decrement during the placebo session. Participants had no trouble accurately estimating their performance on cognitive tests under modafinil or placebo. While under the modafinil treatments, few participants experienced increases in fatigue or drowsiness compared to placebo, while a greater than chance number experienced increases in dry mouth, tingling and nervousness under the 400 mg dose. As expected, oral temperature, heart rate and blood pressure were significantly higher during the early morning hours in the modafinil treatments as compared to placebo. Participants drank more fluids under modafinil as well.

Conclusion: In this overnight, sleep-loss study, modafinil attenuated fatigue effects on cognitive performance without producing overconfidence, while demonstrating no negative vestibular effects. Expected minimal subjective and physiologic symptoms were mild.

AN ASSESSMENT OF MODAFINIL FOR VESTIBULAR AND AVIATION-RELATED EFFECTS

INTRODUCTION

Since at least World War II, amphetamines have been used within military operations when the need for warfighter performance was high and the opportunity for maintaining an appropriate wake/sleep cycle was low. However, amphetamine enhanced performance, can result in numerous side effects, e.g. nervousness, false feelings of well-being, dizziness, tremor, cardiac irregularities, insomnia, addiction, and others (MedlinePlus, 2004).

In December 1998, the pharmaceutical company Cephalon received Federal Drug Administration approval to market modafinil, a new vigilance-enhancing drug, for the management of narcolepsy. This drug belongs to a new group of drugs, *Eugregorics*, under development for over ten years prior to being marketed in France in 1993. These drugs mimic the effects of amphetamines by producing a very high quality of wakefulness, but lack the typical negative side effects associated with amphetamines (Lagarde, Batéjat, Van Beers, Sarafian & Pradella, 1995). Thus, modafinil was thought to hold promise as an effective stimulant for military personnel assigned to sustained operations without the common side effects associated with dextroamphetamine.

Modafinil has been shown across many studies to maintain cognitive performance with very few side effects. Results from Bensimon, Benoit, Lacomblez, Weiler, et al. (1991) indicated that modafinil prevented a deterioration of cognitive performance in most tasks 6 hours after the drug was administered, and minor improvements were seen 18 hours after administration. Tasks performed include reaction time, short and long term memory exercises, as well as critical flicker fusion. Lagarde and Batéjat (1995) found that participants performed better across all tasks under modafinil. Although it was noted that some tasks were more sensitive to sleep deprivation than others, modafinil still maintained superior performance during the sleep deprivation on the following tasks: reaction time task, mathematical processing, memory search, spatial processing, unstable tracking, and grammatical reasoning. Baranski, Cian, Esquivie, Pigeau, and Raphel (1998) administered a cognitive test battery during a period of sleep deprivation, and used three different groups at three different doses over 24 hours to investigate what effect modafinil would have at maintaining performance levels. The 300 mg treatment maintained participants at near base-line levels, the 150 mg dose provided some relief, and the 50 mg dose was not statistically different form the placebo control group.

The mechanism of modafinil is not yet fully understood, however, modafinil-induced wakefulness can be attenuated by the alpha-1 adrenergic receptor antagonist like prazosin. Conversely, modafinil is not involved in assay systems known to be responsive to alpha adrenergic agonists (Cephalon, 2004). Lin, Hou, Rambert and Jouvet (1997) found modafinil both chemically and pharmacologically different from amphetamines in that modafinil produced long lasting waking effects without behavioral modification, addictive attributes, or sleep rebound. In addition to its lack of adverse effects, modafinil exhibits a terminal half-life of 9-14 hrs with peak blood concentrations 2-4 hrs after absorption with an oral clearance

of 50-60 ml/min, which makes it a prime candidate for field use (Wong, Gorman, McCormick, & Grebow, 1997).

The majority of empirical research with modafinil has been based upon trials of 200 or 400 mg/day, therefore we also examined these two levels of drug administration. A study by Lagarde et al. (1995) showed 200 mg administered every eight hours enhanced vigilance during sixty hours of sleep deprivation. In a study by Baranski, et al. (1998), participants given a dosage of 100 mg every eight hours maintained cognitive performance levels throughout 64 hours of sleep deprivation. This study found that doses of 50 mg every eight hours did not bolster cognitive performance. Participants given 50 mg every eight hours maintained non-significant performance improvement, and those participants given 16.7 mg every eight hours showed cognitive decrements similar to the placebo group. This study asserts that 100 mg every eight hours was the required minimum dose to maintain cognitive performance during periods of prolonged periods of sleep deprivation. Batéjat and Lagarde (1999) found that a 200 mg dose of modafinil administered every eight hours improved performance on tasks affected by limited sleep depravation.

Additional sleep deprivation studies conducted using modafinil also asserted its beneficial properties (Warot, Corruble, Payan, Weil, et al., 1993; Lagarde & Batéjat, 1995). Stivalet, Esquivie & Barraud (1998) studied the effects of modafinil on attentional processing during 60 hours of sleep deprivation. Participants were given a total of 300 mg/day in 100 mg doses every 8 hours. Results indicated that modafinil prevented slowing of serial processing and prevented normal increases in the rate of error during the period of sleep deprivation. Bensimon et al. (1991) used psychomotor tasks, reaction time, and memory evaluations to demonstrate the efficacy of modafinil. Results showed that modafinil prevented severe cognitive impairment during the sleep deprivation period 6 hours after the drug was administered; marginal positive effects were seen at 18 hours.

Morehouse, Broughton, Fleming, George, Hill, et al. (1997) conducted research into possible unfavorable side effects of modafinil during a six week study of 71 narcoleptic patients. In a completely within-subject study, patients received doses of 200 or 400 mg/day of modafinil. Overall, 52 adverse effects were reported under the 200 mg condition, but none was found to be statistically different the placebo condition. A higher number of complaints of nervousness and nausea were reported in the 400 mg/day group, although this was not statistically different from the 200 mg/day group. In clinical trials comparing doses of 200, 300, and 400 mg/day of modafinil, headache and anxiety were the only two side effects clearly related to dosage (Cephalon, 2004).

Baranski and Pigeau (1997) found that modafinil produced "a disruptive effect on self-monitoring, inducing a reliable 'overconfidence' effect which was particularly marked 2-4 hours post-dose." Batéjat and Lagarde (1999) also reported modafinil-related changes in self-confidence. It was for this reason that the present investigation assessed the impact of modafinil on overconfidence. Findings reported by Pigeau, Naitoh, Buguet, McCann, Baranski, Taylor, Thompson, & Mack (1995) indicated an increased frequency of urination when compared to dextroamphetamine or placebo. This could indicate a diuretic effect

similar to caffeine. The present investigation compared fluid intake and urine output to look for such an effect.

Modafinil induces (causes the formation of) the CYP3A4 isoenzyme. CYP3A4 metabolizes modafinil, as well as steroidal compounds such as oral contraceptives, cyclosporine, erythromycin and theophylline. Pharmacokinetic testing indicated higher CYP3A4 activity in young females as compared with young males, at a ratio of 1.4:1. This results in a shorter half-life for modafinil in young females, at a mean of 9.7 ± 1.7 hours, versus a mean of 11.5 ± 2.4 hours in young males. The operational implications of this include:

1. Advising females to use alternative contraception while taking modafinil (this is akin to the advice given for concomitant antibiotics and oral contraceptive use).
2. A different dosing schedule for females if more than 8 hours performance maintenance/improvement is required.
3. Consideration of prescribing antibiotics other than macrolides for treatment of infections when used concomitantly with modafinil for an extended period of time.

Modafinil studies have also examined sleep rebound effects. Batéjat and Lagarde (1999) examined napping and modafinil as two countermeasures for fatigue. Results indicated that both were beneficial, and demonstrated that modafinil did not prevent sleep, as found with the use of amphetamines. Two studies used modafinil during prolonged sleep deprivation and then measured sleep rebound parameters with polysomnography for two nights afterward. Lagarde et al. (1995) found that modafinil at 600 mg/day levels produced a sleep rebound effect on the second post-treatment night. Buguet, Montemayeur, Pigeau and Naitoh (1995) showed that modafinil in 300 mg/day levels did not produce any sleep rebound effect.

In a clinical trial reported by Cephalon (2004), a total of 151 protocol-specified doses ranging from 1000 to 1600 mg/day were administered to 32 participants, including 13 participants who received doses of 1000 or 1200 mg/day for 7 to 21 consecutive days. In addition, several intentional acute overdoses occurred; the two largest being 4500 mg and 4000 mg taken by two participating in foreign depression studies. None of these study participants experienced any unexpected or life threatening effects. Adverse experiences that were reported at these elevated doses included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. Other observed effects included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea and decreased prothrombin time; however, patients fully recovered from these adverse effects by the following day (Cephalon 2004).

The performance and side effects produced by modafinil have been the focus of recent studies. Perhaps the most applicable study was that conducted at USAARL by Caldwell, Smythe, Caldwell, Hall, Norman, Prazinko, Estrada, Johnson, Crowley, Brock (1999). Pilot participants in his study reported potential vestibular effects, most frequently dizziness, during and after their tasks in a motion based flight simulator. Although this study was not designed specifically to investigate vestibular interactions, Caldwell noted that the reported effects might have been attributable to the dosage given (400 mg total) or to the motion of the simulator coupled with computer-based scenery models. Sleep deprivation has been

shown previously to impair vestibular responses (Collins, 1988). Since this side effect has not been reported in other modafinil studies, it seemed possible that this adverse effect was dose related, exacerbated by a participant's predisposition for motion sickness, or the result of sleep deprivation alone. The present investigation specifically sought to assess the effects, or lack of effects, of modafinil on dynamic and static vestibular function as it might relate to pilot performance.

Generally, previous studies have indicated that modafinil was relatively benign. The most commonly reported side effects were headache, nervousness, nausea, and dry mouth. Morehouse et al. (1997) suggested that participants could have developed some tolerance to these adverse side effects over time. Overall this drug was well tolerated and the occurrence of a medically significant event from the drug alone was not likely. However, to manage this risk, participants in our study completed a symptom survey and had their vital signs (blood pressure, temperature, and pulse) taken hourly.

The ideal countermeasure to fatigue is to obtain adequate sleep. This can happen if all duty days and crew rest hours follow current regulations. However, both nighttime and combat operations frequently extend duty days to dangerously long duration or prevent crew rest from being restorative. In such cases, it is imperative that techniques be made available that will reduce operational risks by sustaining acceptable levels of human vigilance and cognition. A recent study of Canadian C-130 pilots demonstrated, with in-flight performance measures, that crews on long duration missions experience shortened sleep patterns and significant decreases in alertness and performance (Paul, Pigeau, & Weinberg, 2001). During OPERATION DESERT STORM, modafinil was distributed to French military personnel but was taken irregularly and with only informal reporting of benefit or side effects. The Air Force's Air Expeditionary Force Battle Laboratory at Mountain Home AFB, Idaho, was extremely interested in the possible use of modafinil to promote cognitive performance during long duration missions. However, it could not be used without a thorough investigation of the potential side effects associated with varied doses. The present investigation evaluated a stimulant that had received sufficient laboratory study to make it appealing to military medicine but had not been tested thoroughly enough to determine whether the potential side effects would prohibit its use in aviation applications.

We examined one "safe to fly" aspect of this pharmacological aid: the potential for vestibular disturbance associated with the use of modafinil. In addition, efficacy was assessed through performance testing and self-reports of sleepiness. Overconfidence and diuresis were also assessed. Cognitive improvement had been noted at 200 mg modafinil, with anecdotal findings (Caldwell, Smythe, Leduc, & Caldwell, 2000) reporting possible vertigo following a second 200 mg dose. This protocol used single-dose modafinil at both 200 mg and 400 mg.

Hypotheses

1. The effects of modafinil 200 and 400 mg on vestibular function, cognitive and vigilance performance, self-reports of sleepiness and confidence, and diuresis will differ from placebo

2. The effects of modafinil 200 mg and modafinil 400 mg on vestibular function, cognitive and vigilance performance, self-reports of sleepiness and confidence, and diuresis will differ from each other.

We expected that the cognitive tests would show a typical fatigue effect early in the morning, 0200-0600, in the placebo treatment when compared to evening baseline measures. We also expected that modafinil would ameliorate the fatigue effect compared to placebo. By responses for 200 mg and 400 mg administrations, we hoped that the data would help us determine dosages for more thorough studies in the future involving AF pilots, simulated flying missions, and possible field studies.

METHODS

Experimental Design

The experimental design was multi-factorial with repeated measures across two levels of the Drug/Fatigue treatment (1, evening, pre-drug and 2, early morning, post-drug) and three levels of Dose (0, 200 and 400 mg). Males and females were counterbalanced as well as the order of vestibular testing (Rotary Chair, Force Platform, Visual Testing versus Force Platform, Visual Testing, Rotary Chair). For assessments of the Vestibulo-Ocular Reflex (VOR), we used a third, 4-level repeated-measures factor, rotational frequency (1, 4, 16, and 32 deg/sec). We presented the modafinil doses in three of six possible dose orders by participant group, a Latin Square (placebo-200-400, 200-400-placebo, and 400-placebo-200); thus, we also were able to assess effects across weeks. Simple effects were assessed post hoc by multiple t-tests. Cognitive testing, vigilance testing, subjective surveys, etc. were conducted before and after the vestibular tests and were analyzed by breaking down the condition variables into trials. Trial 1 was in the evening, pre-drug before the vestibular testing and Trial 2 was after vestibular testing. Trial 3 was in the early morning and post-drug, before the vestibular testing. Trial 4 was after the vestibular testing.

Sample Size and Test Power

We assumed that a mean deviation outside of approximately one standard deviation unit was required before an effect could be judged to be meaningful. Thus, the experiment was designed to be sensitive to a 1-standard-deviation effect size for a two-tailed test at a confidence level of 95% (alpha = 0.05) and a power of (1 - beta =) 96% (Cohen, 1988, table 2.3.2, formula 12.2.1) when r = 0.50 for repeated measures within Factor A (ibid., formula 2.3.9). This design required a sample size of 15.

Participants

The Brooks AFB Institutional Review Board reviewed the benefits and risks in the research protocol and its associated informed consent process. The protocol was approved and received the Air Force Surgeon General's identifier, FBR-2000-035H. Participants were recruited through an existing Wyle Laboratories list of potential participants from the San

Antonio area. NTI personnel conducted all recruiting and screening of participants, with Wyle Laboratories handling the insurance issues, payment of participants, and medical examinations of participants. The participants consisted of 18 healthy males and females, aged 22-50, participating in three groups of six. They were paid $12 per hour to participate. All candidate participants were screened medically to determine if the ingestion of modafinil would cause any harm or possible complications. Also, all participants were notified of known modafinil side effects and understood that a medical consultant was available throughout the entire study.

Screening evaluation

There were a total of five steps in the screening evaluation process. The process included: 1) A Recruitment Questionnaire to qualify potential participants; 2) an Informed Consent information meeting to brief potential participants prior to voluntary signing of the Informed Consent Document (ICD); 3) a Medical Questionnaire; 4) a Participant Personal Information Sheet and Medical Review to verify the information provided in the Medical Questionnaire; and 5) a Standard Physical Examination and drug screening. This process was developed to document the personal and medical background information provided by each participant. NTI, Inc. conducted Steps 1-4, and Wyle Laboratories completed Step 5.

The confidentiality of all questionnaires was a prime concern of the investigators. Questionnaires and other data did not contain the name of the participant or any other personal identifying information. Rather, the only identifying information was contained on the ICD and the Participant Personal Information Sheet. These sheets were the only links between the participant and his/her code number. These sheets were kept together and locked up when not in use by the investigators and were not made available outside the investigative team.

Facility

The USAFSAM/FECA Auditory Facility in the basement of Building 125, Brooks AFB TX, consisted of a set of laboratory testing rooms, a computer laboratory, an electronics laboratory, a patient waiting room, and offices. Restrooms were immediately outside the Auditory Facility. The experimental data were collected from the participants in the testing rooms, the computer laboratory, and the electronics laboratory. An adjacent conference room was configured to accommodate participants on their short breaks, under supervision. The participants were in one of these rooms during the entire 12 hours or accompanied to the restrooms. A minimum of four investigators was present at all times in the facility during testing. After the equipment had been tested in the configuration required for the experiment, the Laboratory Safety Engineer inspected the entire facility for participant safety.

Visual-Vestibular Function Testing

The human visual and vestibular sensory systems are critical to our normal everyday activities and are co-dependent. Thus, to properly assess one system requires that both be analyzed. The tests we selected were non-invasive, functional tests of these systems. The word functional should be emphasized, for the tests were not designed to identify

pathologies. The assessment of the "vestibular" effects of modafinil was actually carried out at four levels of central nervous system control function: visual (saccadic eye movements, smooth pursuit eye movements), vestibular (vestibulo-ocular reflex), visual-vestibular (optokinetic response), and visual-vestibular-somatic (postural stability; Shepherd, 1994; Westmoreland, Benarroch, Daube, Reagan & Sandok, 1994). This battery of tests (except postural stability) had been validated on normal participants (Engelken, Stevens, Bell & Enderle,1993; Engelken, Stevens, Bell & Enderle, 1994; Engelken, Stevens, Mcqueen & Enderle, 1995; Engelken, Stevens & Mcqueen, 1996). Further analysis on a group of 100 young and healthy Air Force pilot candidates determined normal response ranges.

Visual: Saccadic Eye Movements

Saccadic (jumping) eye movements are ballistic movements that aid the visual examination of near objects; saccades are prominent during reading. They are controlled by the frontal eye fields of the cortex, located in the posterior portion of the middle front gyrus of the cortex (Brodmann area 8). Frontal, eye-field control operates, via the pontine paramedian reticular formation, on the oculomotor nuclei (oculomotor, trochlear, abducens) and then via the respective cranial nerves (3, 4, 6) on the extraocular muscles. The vestibular system is not involved in the control of saccades.

In the saccade test, following the smooth pursuit test, the participant was asked again to fixate on the small spot of light. The light stayed in one position for approximately two seconds then reappeared instantly in another position (one of eight positions selected pseudo-randomly). The participant was to acquire the spot as quickly as possible and fixate on it in the new position. The entire test consisted of 80 target moves of 5 through 40 degrees of visual angle, in multiples of 5-deg increments. The eye movement responses were recorded using the infrared reflectance technique at 1000 samples per sec. Mean saccade latency was the variable assessed for all saccades. Also, for saccades within the range of 20-30 deg of visual angle, we computed peak and mean velocity. Unweighted means were calculated across the means for individual eye data (left, right), direction, and amplitude,thus reducing to a single mean within trials, within doses.

Visual: Smooth Pursuit Tracking

The parieto-occipital eye fields of the visual cortex control smooth-pursuit, eye movements. These fields are located at the parieto-occipital junction in each hemisphere (Brodmann area 19). Fibers project from area 19 to the superior colliculus, and from there to the reticular formation. In the reticular formation, they join with vestibular projections from the vestibular nucleus and the cerebellum to influence the oculomotor nuclei (oculomotor, trochlear, abducens) and then, via the respective cranial nerves (3, 4, 6) to the extraocular muscles. Smooth pursuit tracking was classified under the visual level because the head is held stationary preventing vestibular input in our tracking test.

Each participant was asked to track a small spot of light moving sinusoidally in the horizontal plane at eye level (+/- 20 deg). The eye movement responses were recorded using the infrared reflectance technique at 125 samples per sec, as above, and separated into smooth and saccadic components. The smooth component was decomposed through linear systems analysis to compute gain and phase responses with respect to the stimulus, and left-

right eye asymmetries (Engelken, Stevens & Bell, 1994). The saccadic component of smooth pursuit eye movements was quantified by calculating the percentage of the total tracking movement contributed by the saccadic system, with a smaller saccadic component representing better performance of the smooth pursuit system (Engelken, et al., 1994). Unweighted means were calculated across the means for eye(s) used (left, right, both) and across the means for individual eye data (left, right), reducing these six means to a single mean within trials, within doses. The phase response data were not analyzed because, during the clinical development of these tests, it was found that the saccadic component was a much better indicator of smooth pursuit degradation than phase (Engelken, et al., 1994); in fact, in some cases where the smooth pursuit gain was extremely low and the percent of saccadic tracking was very high, phase was hardly affected.

Vestibular: Vestibulo-Ocular Reflex (VOR)

When the head is rotated, signals from the semicircular canals and the otolith, two sensory organs of the ear associated with maintaining body equilibrium, cause the eyes to compensate by moving in the opposite direction with equal force to the motion of the head or body. This is referred to as the vestibulo-ocular reflex. This reflex allows one to fixate and hold a visual object while turning the head. It is an open loop with respect to visual feedback; it receives no visual input. It operates di-synaptically from the vestibular apparatus to the oculomotor nuclei (oculomotor, trochlear, abducens) and then, via the respective cranial nerves (3, 4, 6), to the extraocular muscles. A polysynaptic, supplementary pathway exists from the vestibular nucleus through the reticular formation to the oculomotor nuclei. Another polysynaptic pathway starts from the vestibular nucleus, goes through the cerebellum and reticular formation and terminates at the oculomotor nuclei.

The VOR test was accomplished by rotating the seated participant continuously about the body's vertical midline in complete darkness. (During continuous rotation, VOR eye movements are interspersed with re-fixation (fast phase) movements called nystagmus eye movements.) Because the participant had no visual stimulation, seeing nothing but darkness, the lack of visual stimulation allowed the di-synaptic reflex responses from the vestibular system to be isolated. The VOR eye movements were measured using standard electro-oculographic techniques at 128 samples per second and yielded angular eye positions. The critical dependent measures assessed included the gain and phase response of the slow phase eye velocity in relation to the forcing functions (0.01, 0.04., 0.16, and 0.32 Hz with peak velocities 60 deg/sec). The symmetry of the two eyes' responses was also assessed. (Due to statistical package limitations we did not assess the eye measures at .02 and .08 Hz, though the data were collected.)

Visual-Vestibular: Optokinetic Response (OKN)

The OKN response provides a measure of the reflex visual tracking capability when the head is fixed and the entire visual surround is in motion (Engelken & Stevens,1990). The OKN response holds the image steady on the retina for as long as possible. The OKN response is controlled in the same manner as smooth pursuit eye movements (above).

The participant, seated in the VOR apparatus (above), was held stationary while a pattern of stripes (3.45 deg shadow + 7.8 deg light) was projected onto the wall of the enclosure. The

pattern began to move and increased in velocity to 100 deg/sec at a rate of 2 deg/sec/sec. The participant was instructed to keep the pattern in focus as long as possible. (Again, during continuous visual field movement, OKN response eye movements are interspersed with nystagmus eye movements.) The participant's slow-phase velocity response (i.e., non-nystagmus response) to the stimulus was expected to follow a 2-deg/sec rectilinear ramp paralleling the changing stimulus. The response velocity at which linearity fell off by more than 10% was the "fall off" velocity. A fall off velocity of 70-deg/sec represented better visuo-vestibular performance than a fall off velocity of 30-deg/sec. Each participant was tested twice in each direction with the best of the two performances recorded as the score for each direction. One variable was assessed: mean lateral fall-off velocity. There were two missing data points: Participant 3, Week 1 (Dose 0), Trial 2, and Participant 10, Week 3 (Dose 0), Trial 2. Note that these were the same dose and trial across the two participants. These two values were replaced with the grand mean fall-off velocity, 49.58-deg/sec. Unweighted means were calculated across the means for the two directions of eye movement (left, right), reversing the sign of negative values and reducing these two means to a single mean within trials, within Doses or Orders.

Visual-Vestibular-Somatic (Postural Stability)

Our force platform measurement of postural stability required the participant to stand upon a platform that measures change in the body's center of pressure over time. The changes in the body's center of pressure reflect an integration of somatosensory function, with and without visual function, and the static component of vestibular function provided by the otolith organs of the inner ear. These measurements have been used previously to analyze postural stability after alcohol ingestion (Kubo, Sakata, Matsunaga, Koshimune, Sakai, Ameno, & Ijiri, 1989), benzodiazepine administration (Patat & Foulhoux, 1985), and prolonged exposure to microgravity (Collins, De Luca, Pavlik, Roy, & Emley, 1995). The participants' posture was heels together, feet open at a 30-deg angle, and hands at sides, much like a relaxed version of the military position of attention. The participants were told the elapsed time every 15 seconds. Two minutes of data were collected for both eyes open and eyes closed conditions, at a sampling rate of 10 Hz. The two-minute data series was divided into four 30-sec epochs for analysis. The measure assessed was the area (cm^2) of the ellipse that captured 95% of the center of pressure measures for each epoch.

Sleep deprivation, itself, might cause participants to report dizziness anecdotally. This investigation was designed to allow such an effect to be quantified, if present. We anticipated that there might be a significant increase in reports of dizziness and poorer vestibular test scores during the early morning hours in the placebo group compared to baseline, evening measures. This study was designed to determine if the effect with modafinil was significantly worse than with placebo. If these negative effects were present with modafinil, then we would certainly suggest that the drug should not be used in aviators without further study.

Performance Testing

The performance tests were used to examine simple cognitive performance and fatigue. They included the Matching to Sample Task, the Two Choice Reaction Time Test, Tapping

and the Psychomotor Vigilance Task. Additionally a desktop flight simulator was provided as a filler task to keep the participants awake and engaged when other data were not being collected. The cognitive test schedule was designed to maintain a continuous work environment, preventing participants from napping.

Schlegel, Shehab, Gilliland, Eddy and Schiflett (1995) calculated intertrial correlations (differential stability) and Load and Novick (1968) reliabilities for the essential cognitive performance tests proposed for this study. Load and Novick reliabilities were computed by 1) subtracting the Within-participant Variability from the Between-participant Variability, 2) the difference divided by the Between-participant Variability. The ratios computed for these tests had similar magnitudes and paralleled the intertrial correlations. At least one measure on each of the cognitive tests had a very good to excellent level of differential stability and reliability (typically 0.80 or above). These cognitive tests have shown performance effects in space with N=6 (Eddy, Schiflett, Schlegel, & Shehab, 1999).

Cognitive Tasks

A cognitive performance test battery was implemented on desktop personal computers in the Windows® operating system using the Navy's Automated Neuropsychological Assessment Metric (ANAM). It consisted of a library of tests and batteries designed for a broad spectrum of clinical and research applications. This library of computerized tests was constructed to meet the need for measurement of cognitive processing efficiency in a variety of psychological assessment contexts that include neuropsychology, fitness for duty, neurotoxicology, pharmacology, and human factors research (Reeves, Winter, Kane, Elsmore, & Bleiberg, 2001).

Three tests from the Automated Neuropsychological Assessment Metrics (ANAM) were administered five times throughout each night of the study. Trials one and two occurred before and after the vestibular testing and before drug administration. Trials 3 and 4 occurred before and after the vestibular testing, and after drug administration. Trial 5 occurred at 0530, thirty minutes before participants were dismissed. The three tests are listed below in order of presentation.

Delayed Matching-to-Sample Task: This test required a left or right click corresponding to a left-right choice between two patterns, one of which matched a single pattern presented 5.0 to 5.1 seconds previously. The probe duration was set to 3000 ms, delay duration was set to 5000 to 5100 ms, and timeout occurred at 3100 ms. Task duration was three minutes. The pattern structure was a four-by-four grid, within which eight cells were colored red and eight were colored aqua, in quasi-random patterns.

Two Choice Reaction Time Test: This test presented two stimuli (+ and *) individually. When each stimulus was presented, participants had to press a specified corresponding mouse button. The test lasted for 3 minutes.

Tapping: For this test, participants were required to tap the left mouse button with their index finger as fast as they could. The test lasted 10 seconds.

Vigilance

Vigilance performance was assessed using the Psychomotor Vigilance Task (PVT; Dinges, 1992; Vigilance Task Monitor, Model PVT-192, CWE, Inc., Ardmore PA, available from Ambulatory Monitoring, Inc., Ardsley NY). The PVT required sustained attention and discrete motor responses. It was a brief, high signal load, reaction time task that was sensitive to many minor cognitive stresses, including fatigue due to sleep loss, circadian variation, and shift work. It is an extension of the Unprepared Simple Reaction Time Task. The task is easily learned and quite sensitive to sleep disruption and fatigue. It proved to be sensitive and reliable in field studies of fatigue in commercial truck drivers (Wylie, Shultz, Miller, Mitler, & Mackie, 1996) and US Coast Guard crewmembers (Miller, Smith, & McCauley, 1998).

The 8" x 4.5" x 2.4" portable, battery-operated device ran a continuous simple reaction time test for ten minutes. The participant's job was to watch a digital counter on the device and, when the counter started to run, to turn off the counter as quickly as possible. A relatively quick response was about 200 msec. The task provided a relatively pure demand for sustained, focused attention. The task was presented in the visual-only (0.5-inch LED) mode. The variables provided by the PVT-192 included the number of stimuli presented, the mean of the reciprocals of all reaction times, the mean of the reciprocal of the slowest 10% of reaction times, the number of false alarms, and the number of lapses (reaction times slower than 500 msec) (Dinges, Pack, Williams, Gillen, Powell, Ott, Aptowicz, & Pack, 1997).

Subjective Measures

Measures of Overconfidence or Impulsiveness

Our approach to measuring overconfidence emulated the method reported by Caldwell et al. (2000). Participant overconfidence was assessed by asking the participants to estimate their performance expectation prior to performing a cognitive test. For each of the three tasks (Two Choice Reaction Time Test, Matching to Sample Task, and the Tapping Task), participants were asked to predict if their scores would be better, the same, or worse than their previous trial. They were then asked to predict an estimated percent correct and an estimated reaction time for the Two Choice Reaction Time Test and the Matching to Sample Task, and the number of taps for the Tapping Task. At the end of each task participants were presented feedback. This feedback consisted of average response time and accuracy for the Two Choice Task and the Matching Task, and number of taps for the Tapping task. The over- or under-estimates were compared with actual performance levels recorded for each test; a delta score was calculated for analysis.

Stanford Sleepiness Scale (SSS)

According to Mitler, Carskadon MA, & Hirshkowitz (2000), the "Advantages of the SSS include its brevity and ease of administration and the fact that it can be administered repeatedly. Experimentally-induced sleep deprivation increases SSS scores; however, normative data do not exist." The SSS usually correlates with standard measures of performance. However, the extreme values on the scale are used infrequently and the rank-ordered statements overlap several perceptual dimensions including sleepiness-wakefulness, alertness and concentration. Horne (1991) suggested parallelism between the SSS and the

alertness-sleepiness descriptors used for the "vigor" factor of the Profile of Mood States (POMS). The POMS vigor scale has also demonstrated sensitivity and reliability with respect to quantifying perceptions of sleepiness. To use the SSS (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973), the participant selects one of seven sets of Likert-scale descriptors, ranging from 1, "Feeling active and vital; alert; wide awake," to 7, "Almost in reverie; sleep onset soon; lost struggle to remain awake." A rating of 5 or above is often cause for concern with respect to acceptable job performance. A SSS rating is acquired from the participants every few hours while they are awake. We acquired the SSS score for analyses of sleep quality and circadian variation.

Symptom Surveys

The participants completed two symptom surveys that were given together four times per night, both before and after vestibular testing.

The WFC Drug Symptoms Checklist. The WFC Drug Symptoms Checklist was created by JA Gibbons and PA Hickey and is shown in Appendix C. It contained 56 items with seven rating levels for each item. It also asked if the drug was perceived to be the source of symptoms and if the symptoms would interfere with job performance. The checklist was used to acquire data about the perceived effects of modafinil.

Vestibular Symptoms Checklist. The Vestibular Symptoms Checklist included 26 items with four rating levels for each item. It is based upon the motion sickness symptomatology checklist of Robert Kennedy's Simulator Sickness Questionnaire (Kennedy, Lane, Berbaum, & Lilienthal, 1993). The checklist was used to acquire data about the combined effects of fatigue, vestibular testing and modafinil. The checklist was scored according to the Simulator Sickness Questionnaire from which it was derived. A total score as well as subscores for nausea, oculomotor, and disorientation symptoms were calculated.

Other Physiological Measures

Vital Signs

Blood pressure, temperature, and heart rate were recorded eight times per night to assess some of the physiological effects of the drug, before and frequently after administration. A standard blood pressure cuff and oral thermometer were used. In addition, as directed in AFRL/HEP Operating Instruction 44-119 *Medical Education and Research: Human Subjects in Research*, any measurement exceeding the following values required notification of the medical monitor.

- Systolic Blood Pressure greater than 160 mm Hg
- Diastolic Blood Pressure greater than 100 mm Hg
- Pulse greater than 110 beats per minute
- Temperature greater than 101.5° F (38.6° C) orally

Urinalyses

We hypothesized (h_1) that urine output affected by modafinil would increase compared to placebo. The urine was also assayed for the presence of modafinil.

Pigeau et al (1995) found that frequent urination was the side effect reported most often with modafinil usage. However this side effect may have been recorded for the same participant more than once; since fluid intake and output were not controlled or recorded. Thus, the actual occurrence of frequent urination in a given population could not be extrapolated from these data. From Cephalon, 2004, no data appear to have been submitted to the FDA showing any significant incidence of frequent urination. Nonetheless, frequent urination is undesirable during operations and may be associated with dehydration if urine output is sufficient. Urine output can be affected not only by stimulants such as caffeine, but also by increased fluid intake. A limitation of this experiment was an inability to control the fluid intake of participants prior to the testing period. Therefore, accurate 24-hour fluid intake and output could not be determined.

However, monitoring the urine output during the experimental period allowed for a measure of change after the administration of modafinil, which occurred about 5.5 hours into the testing period. This 5.5 hours plus the approximately 2-hour delay from ingestion to onset of peak effect for modafinil provided about a 7.5-hour buffer before possible increased urinary output or frequency due to modafinil was expected. The 7.5-hour period also allowed most fluid taken in prior to the experimental period to clear the body prior to the time at which any effect of modafinil was expected.

All test participants used graduated containers for their beverages. Fluid intake during the testing period was measured by periodic checks of the containers and manual recording of volumes consumed. All urine output was collected. The urine volume, specific gravity and temperature (to verify that the urine specimens were not diluted with a cooler liquid, such as tap water) were recorded immediately after voiding, an aliquot (60 ml) was taken from the first voided specimen after 01:30 hours for subsequent analysis, and the remainder of the urine was discarded.

The urine aliquots were assayed for the presence of modafinil. The assay method used was based upon high performance liquid chromatography (HPLC) and was developed and validated by staff at the Clinical Research, Wilford Hall Medical Center, Lackland AFB, Texas[1]. One 100-mg modafinil tablet was used to prepare the modafinil stock standard (1.0 mg/mL) in methanol. The sample was mixed on an Eberbach shaker, centrifuged and the methanol was decanted and stored at 4 ± 3 °C. Modafinil urine standards (1.0, 5.0, and 10.0 mg/mL) were prepared from the stock standard. After evaporation of the methanol, several 10-mL aliquots of the negative urine control were added to dissolve the modafinil. The urine pool used for modafinil urine standards and the negative urine standard was prepared with a urine pool analyzed for non-interfering co-extractable substances.

The chromatographic system consisted of a Waters 600E Controller, 717 Autosampler, 996 Photodiode Array Detector (PDA), and a Millennium 2010 Chromatography Manager (Waters, Milford MA). Chromatographic analysis was performed on a Waters Symmetry C-18 reversed phase chromatographic column, 4.6 x 250-mm (Cat. No. WATO 54215). The HPLC mobile phase consisted of methanol:water:acetic acid, 500:500:1, v/v. The HPLC

[1] Schwertner HA, Olsen E. Analysis of modafinil in urine by high-performance liquid-chromatography, Personal communication, March 2002.

operating parameters were as follows: injection volume, 10 mL; column flow rate, 1.0 mL/minute; chromatographic run time, 30.0 minutes; PDA spectra recording, 220 and 233 nm.

Urine samples collected from subjects taking modafinil or placebo during the study were stored at -80°C prior to analysis. Samples were allowed to reach room temperature and 5 mls of each urine test sample were extracted with ethyl acetate. Fifty mg of the acetic acid internal standard (phenylthio) were added to each extracted sample. The extraction solvent was evaporated under nitrogen and after drying, the samples were reconstituted with 700 mL of the mobile phase, mixed and transferred to 700 mL injection inserts.

Accuracy was determined by comparing the concentration of the modafinil urine standards to the modafinil standards in methanol and by examining possible interferences in the five negative urine samples. There was complete resolution between modafinil, the internal standard, and other co-extractable constituents. Modafinil/(phenythio)acetic acid ratios were linear (r ^{3}0.999) over the range of the modafinil urine standards (1.0, 5.0, and 10.0 mg/mL). The within-run precision (CV) of the modafinil urine standards was 2.5% at 220 nm and 5.4% at 233 nm. The lower limit of sensitivity was established at 1.0 mg/mL. This concentration was used to designate positive modafinil urine (^{3}1.0 mg/mL) from negative urine samples (<1.0 mg/mL). A urine modafinil concentration ^{3}1.0 mg/mL confirmed that a subject took modafinil. Subjects with modafinil concentrations <1.0 mg/mL were considered negative and either did not take the drug or the drug was not detectable.

Procedures

Participant Training

The three groups of six participants attended one two-hour orientation and training session prior to testing. This session was held from 1700 to 2100 on Thursday night, the night before the first night of testing. The principal investigator provided a brief welcome and orientation, gave a tour of the facility and showed the testing facilities and equipment to the participants. The participants were trained on the three cognitive tasks and the Stanford Sleepiness Scale within the ANAM test battery. Participants performed each cognitive task 5 times to move them through the steep portion of the learning curve. Because of time constraints, the five participants of group 1 completed the tasks 4 times. The participants' vital signs were also recorded on this evening.

Testing

Each group was then tested on three consecutive Friday nights. Each of the test sessions started at 1800 hours, and ended at 0600 hours the next morning (Saturday).

Drug Administration

During each session, each participant was given a single dose (modafinil 200 mg or 400 mg, or placebo) at approximately 2330 hours. The order of drug treatment was the same within a group, but counterbalanced across the three groups of participants (Table 1).

Table 1. Orders of drug treatment for the three groups of participants.

Group	Week 1	Week 2	Week 3
1	200 mg	400 mg	0 mg
2	0 mg	200 mg	400 mg
3	400 mg	0 mg	200 mg

Participant Instructions

Participants were instructed not to drink alcoholic beverages during the evening prior to or the afternoon of the scheduled session. Caffeinated drinks were not allowed during the testing sessions; decaffeinated soft drinks, water, and juice were offered. Participants were instructed to go to sleep between 2130 and 2200 hours the night before the scheduled test session, to awaken between 0600 and 0700 hours, and to refrain from napping that day. These instructions were intended to reduce variability in the amount of sleep obtained prior to the test session. Participants were also asked to attempt their best performance at all times during the study sessions.

Test Session Procedure

Each group of six participants arrived at 1800 h to eat a light supper, meet with the medical monitor and receive updated instructions, as needed. At 1900 h, they began a round of testing that lasted until 2330 h. During this period, they either flew the flight simulation as a filler task or provided a single set of pre-vestibular-testing measures, vestibular measures and post-vestibular testing measures. The pre-vestibular-testing measures included the Psychomotor Vigilance Task (PVT), cognitive assessment tests (CAT), vital signs (V), and questionnaires (Q). The vestibular measures included, after a minimum of 15 minutes dark adaptation (DA), a period spent in the rotary chair room (RC) for VOR and OKN acquisition, postural sway measures on the force platform (FP), and visual tracking testing (VT). The post-vestibular-testing measures were the same as the pre-vestibular-testing measures (PVT, CAT, V, and Q).

The participants were tested on the sequential schedule shown in Table 2. Half experienced the VOR and OKN procedures before VT and FP was assessed, and half after. This allowed us to test for order effects of the OKN and VOR procedures on postural sway and visual measures.

All participants were given the placebo or one of the two experimental doses (200 mg, 400 mg) at 2330 hours (double blind). Subsequently, they performed the F-PASS filler cognitive tests or were on break until 0100 h. They were expected to reach the projected peak plasma level of modafinil at 0230 h (Wong, Gorman, McCormick, & Grebow, 1997; Provigil® FDA-Approved Draft Labeling, Cephalon, 2004). Their post-drug testing schedule was organized around this time, with vestibular testing occurring between 0145 and 0445 h.

At 0100 h, they began a post-drug round of testing that lasted until 0545 h. As during the pre-drug period, they either flew the F-PASS as a filler task or provided a single set of pre-vestibular-testing measures, vestibular measures and post-vestibular testing measures. Again, the pre-vestibular-testing measures included the PVT, CAT, V, and Q; the vestibular

measures included, after DA, RC for VOR and OKN acquisition, FP, and VT; and the post-vestibular-testing measures were the same as the pre-vestibular-testing measures (PVT, CAT, V, and Q).

The participants were permitted brief unscheduled breaks when necessary (e.g., to use the restroom). They were monitored closely throughout the test session to ensure their wakefulness and were not allowed to sleep, close, or "rest" their eyes at any time during their participation in the study.

Table 2. Subject testing schedule for each set of six participants.

Time	Participants: 1 & 2	3 & 4	5 & 6
1800-1900	Dinner, medical monitor, updates	Same	Same
1900-1915	PVT	F-PASS	F-PASS
1915-1930	V, Q, CAT	F-PASS	F-PASS
1930-1945	Break, S1-DA	F-PASS	F-PASS
1945-2000	S1-RC, S2-VT	F-PASS, Break	F-PASS, Break
2000-2015	S1-RC, S2-FP & DA	PVT	F-PASS
2015-2030	S1-FP, S2-RC	V, Q, CAT	F-PASS
2030-2045	S1-VT, S2-RC	Break, S3-DA	F-PASS
2045-2100	Break	S3-RC, S4-VT	Break
2100-2115	PVT	S3-RC, S4-FP & DA	PVT
2115-2130	V, Q, CAT	S3-FP, S4-RC	V, Q, CAT
2130-2145	F-PASS	S3-VT, S4-RC	Break, S5-DA
2145-2200	F-PASS	Break	S5-RC, S6-VT
2200-2215	F-PASS	PVT	S5-RC, S6-FP & DA
2215-2230	F-PASS, Break	V, Q, CAT	S5-FP, S6-RC
2230-2245	F-PASS	F-PASS	S5-VT, S6-RC
2245-2300	F-PASS	F-PASS	Break
2300-2315	F-PASS	F-PASS	PVT
2315-2330	Break	Break	V, Q, CAT
2330-2345	Drug/Placebo	Same	Same
2345-0000	Break, no food or drink	Same	Same
0000-0015	V	Same	Same
0015-0030	F-PASS	Same	Same
0030-0045	F-PASS	Same	Same
0045-0100	Break	Same	Same
0100-0115	PVT	Break	Break
0115-0130	V, Q, CAT	Break	Break
0130-0145	Break, S1-DA	V	V
0145-0200	S1-RC, S2-VT	Break	Break
0200-0215	S1-RC, S2-FP & DA	PVT	Break
0215-0230	S1-FP, S2-RC	V, Q, CAT	Break

Time	Participants: 1 & 2	3 & 4	5 & 6
0230-0245	S1-VT, S2-RC	Break, S3-DA	Break
0245-0300	V, Break	S3-RC, S4-VT	V, Break
0300-0315	PVT	S3-RC, S4-FP & DA	PVT
0315-0330	V, Q, CAT	S3-FP, S4-RC	V, Q, CAT
0330-0345	Break	S3-VT, S4-RC	Break, S5-DA
0345-0400	Break	V, Break	S5-RC, S6-VT
0400-0415	Break	PVT	S5-RC, S6-FP & DA
0415-0430	V, break	V, Q, CAT	S5-FP, S6-RC
0430-0445	Break	Break	S5-VT, S6-RC
0445-0500	Break	Break	V, break
0500-0515	Break	Break	PVT
0515-0530	V, break	V, break	V, Q, CAT
0530-0545	CAT	Same	Same
0545-0600	Debrief	Same	Same
0600	Depart	Same	Same

Note: PVT = Psychomotor Vigilance Task; CAT = cognitive assessment testing; V = vital signs; Q = questionnaires; RC = rotary chair room; FP = force platform; VT = visual tracking testing; DA = dark adaptation

The testing space was organized into four functions on a single floor and within several co-located rooms. Thus, the participants walked only tens of feet from function to function. The participants reported to and spent their break time in a break room. The PVT, V and Q were administered in a small, quiet room. The F-PASS and CAT were administered in a room that accommodated six computer workstations. Vestibular testing occurred in a 3-part laboratory consisting of the rotary chair room, the vision testing room and the connecting room, which was set up for dark adaptation and postural sway measurement. At least one investigator or proctor, and usually two, were in each functional area when it was in use.

RESULTS

Participant Characteristics

The demographic data on the participant sample is shown in Table 3. There were equal numbers of males and females, four participants were light users of nicotine, 13 participants were in the USAF and 1 person was a shift-worker, but working the day shift throughout the experiment.

Table 3. Participant characteristics.

Parameter	Mean	SD	Range
Age (years)	31.3	5.3	18
Caffeine (drinks/day)	2.2	1.3	4
Alcohol (drinks/week)	2	2.2	7
Education (years)	14.8	1.9	5
Military Service (years)	12.1	5.9	16
Sleep (hours/weekday)	6.5	0.9	3
Sleep (hours/weekend)	8.2	1.7	6

Responses were analyzed excluding three participants. One was unable to continue the study after the first night due to a travel delay. One attended the first two nights of the study but was absent from the third night. One attended all three study nights but reported taking a generic form of Entex LA® (Dura Pharmaceuticals, Inc.; a combination of phenlypropanolamine and guaifenesin) for cough and respiratory congestion on the second night. We removed these three subjects from all analyses (resulting $n = 15$). One participant was removed from the postural sway analysis due to extremely high variability on the force platform. The subject was included in all other analyses.

Visual-Vestibular Function

Vestibular testing was accomplished pre-drug, 1945-2245 hours with post-drug testing 0145-0445 hours. Preliminary analyses did not show any interaction between drugs and factors such as gender or order of vestibular testing. Therefore, analyses reported here will only involve dose levels and time (pre- post drug). Tables 4-6 summarize the statistical results for the Visual-Vestibular Function Section. Post hoc test results are included when the overall F-ratio was significant, $p<0.05$. Main effects were only examined when the Dose by Time interaction was not significant.

Assessment of the data for learning across the three testing sessions revealed slight practice effects for 4 of the 11 vestibular measures. The variables showing some improvement were mean saccade velocity, 10%, peak saccade velocity, 10%, for the saccadic component of Smooth Pursuit Tracking, 14%, and for the A95 measure of the postural sway, 16.7%. As a result, all post-hoc analyses of vestibular data were conducted on changes from the evening, pre-drug baseline. Variables sensitive to fatigue are mentioned even when they are unaffected by the drug treatment.

Visual: Saccadic Eye Movements

Saccadic eye movements were evaluated using saccade latency, peak saccadic velocity and mean saccadic velocity. There was no significant Dose by Time effect on saccade latency, Table 4.

There was no significant Dose by Time effect on peak saccadic velocity, Table 4. As a side note, the pre-drug, evening score was significantly different from the post-drug morning score (regardless of dose) demonstrating the sensitivity of the measure to fatigue effects that were not ameliorated by modafinil. Peak saccadic velocity was reduced by fatigue. Though not significant, there was a trend for peak velocity to be less affected by fatigue the higher the dose of modafinil.

Similar to the results for peak velocity, there was no significant Dose by Time effect on mean saccadic velocity. However, there was a similar significant effect between baseline and early morning scores that appeared to be fatigue related. Mean saccadic velocity was faster during baseline testing as shown in Figure 1.

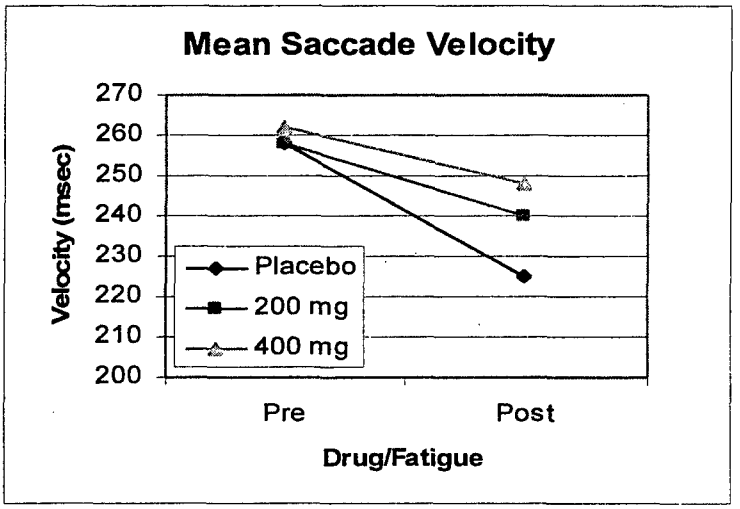

Figure 1. Effect of fatigue on mean saccadic velocity. The trend for modafinil to protect against this fatigue effect was not significant.

Table 4. Summary of Visual Tracking Functional Results

Test/Variable	Dose	Pre-Drug	Post-Drug	Overall F-Ratio[1] and Contrasts[2]
Visual Tracking: Saccadic Eye Movements (msec)				
Saccade Latency	0	$\bar{X}$=211 SD=28.3	$\bar{X}$=213 SD=18.4	Dose: F(2,28)=0.32, *p=0.729* Time: F(1,14)=1.36, *p=0.262* Dose by Time: F(2,28)=0.65, *p=0.529*
	200	$\bar{X}$=209 SD=28.4	$\bar{X}$=216 SD=28.7	
	400	$\bar{X}$=210 SD=26.5	$\bar{X}$=209 SD=25.6	
Peak Saccadic Velocity	0	$\bar{X}$=470 SD=66.2	$\bar{X}$=429 SD=54.4	Dose: F(2,28)=1.29, *p=0.291* Time: F(1,14)=21.65, *p=0.000* Dose by Time: F(2,28)=0.46, *p=0.637*
	200	$\bar{X}$=477 SD=72.2	$\bar{X}$=445 SD=68.7	
	400	$\bar{X}$=483 SD=68.2	$\bar{X}$=458 SD=63.8	
Mean Saccadic Velocity	0	$\bar{X}$=258 SD=39.4	$\bar{X}$=225 SD=31.0	Dose: F(1,20)[3]=1.52, *p=0.240* Time: F(1,14)=33.82, *p=0.000* Dose by Time: F(2,28)=2.54, *p=0.097*
	200	$\bar{X}$=258 SD=37.6	$\bar{X}$=240 SD=37.6	
	400	$\bar{X}$=262 SD=42.2	$\bar{X}$=248 SD=35.5	
Visual Tracking: Smooth Pursuit				
Gain (proportion of forcing function)	0	$\bar{X}$=0.846 SD=0.114	$\bar{X}$=0.790 SD=0.147	Dose by Time: F(2,28)=9.19, *p=0.001* 0 vs 200, SE=0.023, *p=0.002* 0 vs 400, SE=0.031, *p=0.005* 200 vs 400, SE=0.022, *p=0.492*
	200	$\bar{X}$=0.864 SD=0.086	$\bar{X}$=0.894 SD=0.084	
	400	$\bar{X}$=0.833 SD=0.131	$\bar{X}$=0.878 SD=0.108	
Symmetry (degrees/sec)	0	$\bar{X}$=1.16 SD=4.49	$\bar{X}$=2.67 SD=4.96	Dose: F(2,28)=0.36, *p=0.702* Time: F(1,14)=0.00, *p=0.992* Dose by Time: F(2,28)=2.84, *p=0.076*
	200	$\bar{X}$=1.07 SD=2.02	$\bar{X}$=1.17 SD=2.69	
	400	$\bar{X}$=2.42 SD=5.70	$\bar{X}$=0.79 SD=3.71	
Saccadic Component (percentage)	0	$\bar{X}$=17.86 SD=9.21	$\bar{X}$=20.40 SD=12.09	Dose by Time: F(2,28)=9.23, *p=0.001* 0 vs 200, SE=1.612, *p=0.009* 0 vs 400, SE=1.723, *p=0.001* 200 vs 400, SE=1.877, *p=0.205*
	200	$\bar{X}$=14.22 SD=6.72	$\bar{X}$=11.90 SD=6.87	
	400	$\bar{X}$=18.41 SD=11.45	$\bar{X}$=13.60 SD=7.44	

Notes:
1. The F-Ratios for Main Effects are included only when the Dose by Time interaction was not significant.
2. Each Contrast compares pre-to-post change under one dose with change under another dose.
3. Huynh-Feldt adjustment used when Mauchly's test for sphericity failed.

Visual: Smooth Pursuit Tracking

Smooth pursuit tracking was assessed by examining three components of the linear systems analysis decomposition process: gain, left-right eye asymmetry and the percentage of the saccadic component needed to account for the eye's total response to the stimulus. For smooth pursuit gain, there was a significant Dose by Time interaction, see Table 4, as shown in Figure 2. The *post hoc* testing indicated that the pre-to-post gain change in the 200- and 400-mg dose was significantly different than for Placebo. Thus, gain was apparently impaired during the early morning hours with the onset of fatigue, but was protected with the 200- and 400-mg doses of modafinil.

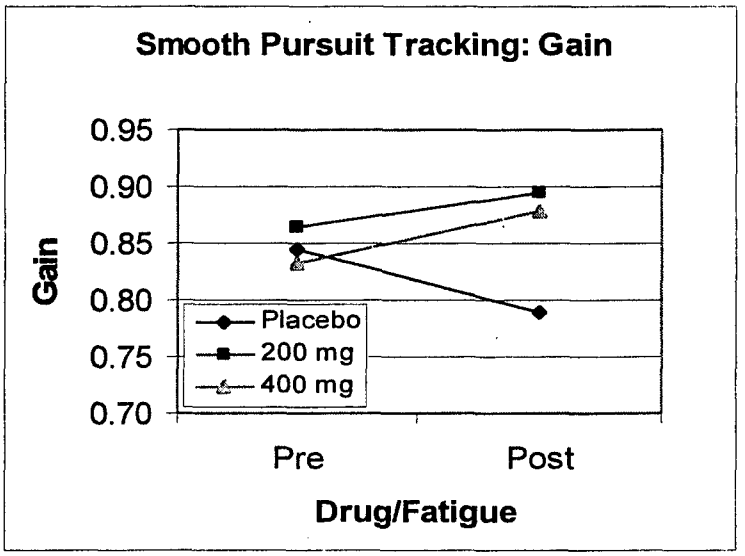

Figure 2. The effect of Dose on smooth pursuit tracking gain (proportion of forcing function) relative to pre-drug baseline.

Smooth pursuit symmetry showed no significant Dose effect (although the interaction approached significance ($p=0.076$)), see Table 4. There was a trend for the eyes to become less symmetrical under fatigue (placebo) relative to baseline whereas under modafinil, symmetry appeared to improve (400 mg) or stay the same (200 mg).

For the saccadic component of smooth pursuit eye movements, the Dose by Time interaction was statistically significant, see Table 4, and is shown in Figure 3. The figure and the *post hoc* assessment suggest that smooth eye tracking begins to degrade under fatigue, but that both modafinil doses maintain performance at baseline levels. Recall that a smaller saccadic component indicates better performance of the smooth pursuit system (Engelken, et al., 1994).

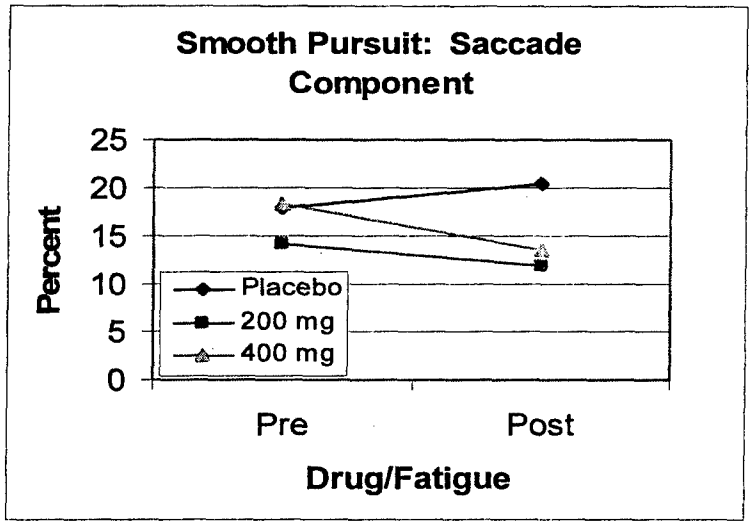

Figure 3. Effect of modafinil on the saccade component of smooth pursuit tracking.

Vestibular: Vestibulo-Ocular Response

The critical dependent measures assessed with the Vestibulo-Ocular Response (VOR) included the gain (proportion of the forcing function signal) and phase response of the slow phase eye velocity in relation to the forcing functions of .01, .04, .16, and .32 Hz. The symmetry of the two eyes' responses was also assessed. Each of the three measures was assessed at each of the four forcing functions separately. The means, standard deviations and F-ratios are shown in Table 5. For gain, the effect of Dose was not significant. However, gain at the lower frequency forcing functions trended toward sensitivity to fatigue effects, though not statistically significant, with the post-drug morning scores (regardless of dose) degrading relative to the pre-drug, evening scores (see Figure 4). Gain at the higher frequencies was unaffected.

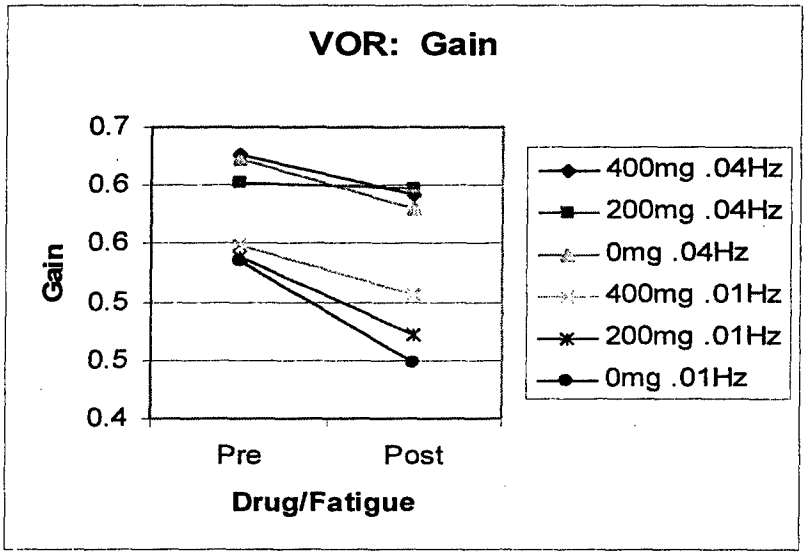

Figure 4. VOR Gain for forcing function 0.01 and 0.04 for each Dose before and after the Drug/Fatigue treatment.

Table 5. Summary of Functional Vestibular Testing: Vestibulo-Ocular Response (VOR) by Variable

Forcing function		Placebo		200		400		Dose by Time Test
		Pre-	Post-	Pre-	Post-	Pre-	Post-	
Gain (proportion of the forcing function signal)								
.01 Hz	$\bar{x}$=	0.535	0.449	0.539	0.473	0.549	0.507	F=(2,28)=1.17,
	SD=	0.148	0.204	0.141	0.168	0.131	0.139	*p=0.310*
.04 Hz	$\bar{x}$=	0.623	0.579	0.601	0.597	0.625	0.591	F=(2,28)=0.28,
	SD=	0.148	0.297	0.141	0.144	0.125	0.141	*p=0.755*
.16 Hz	$\bar{x}$=	0.635	0.684	0.673	0.606	0.667	0.645	F=(2,28)=2.34,
	SD=	0.155	0.280	0.146	0.131	0.144	0.154	*p=0.115*
.32 Hz	$\bar{x}$=	0.629	0.680	0.632	0.604	0.615	0.633	F=(2,28)=0.84,
	SD=	0.159	0.286	0.146	0.177	0.162	0.147	*p=0.415*
Phase Response (degrees/sec, lead or lag)								
.01 Hz	$\bar{x}$=	37.10	40.48	36.76	37.51	36.03	36.96	F=(2,28)=0.93,
	SD=	8.66	7.64	7.80	8.20	6.91	7.80	*p=0.386*
.04 Hz	$\bar{x}$=	11.49	13.53	12.26	10.61	10.45	8.76	F=(2,28)=0.55,
	SD=	5.00	15.32	5.38	6.09	4.69	6.96	*p=0.506*
.16 Hz	$\bar{x}$=	-2.63	-5.01	0.36	-1.18	-1.18	-1.18	F=(2,28)=0.26,
	SD=	10.70	17.42	3.47	5.37	4.02	7.35	*p=0.677*
.32 Hz	$\bar{x}$=	-4.98	-9.33	-3.10	-9.16	-3.63	-2.41	F=(2,28)=1.36,
	SD=	8.76	12.48	4.89	13.82	9.16	3.80	*p=0.267*
Symmetry (degrees/sec, lead or lag)								
.01 Hz	$\bar{x}$=	7.45	7.77	8.47	8.80	3.28	2.74	F=(2,28)=0.03,
	SD=	10.75	12.13	14.98	15.71	12.52	13.69	*p=0.974*
.04 Hz	$\bar{x}$=	2.08	14.45	2.70	7.91	-0.98	3.91	F=(2,28)=0.55,
	SD=	11.47	25.02	15.47	18.00	10.20	16.50	*p=0.585*
.16 Hz	$\bar{x}$=	6.48	2.10	0.47	4.23	2.47	3.20	F=(2,28)=1.10,
	SD=	12.24	16.26	12.25	17.72	9.85	9.17	*p=0.337*
.32 Hz	$\bar{x}$=	3.24	0.35	1.25	4.84	-1.44	1.81	F=(2,28)=1.51,
	SD=	6.48	13.31	9.16	9.32	7.08	10.09	*p=0.238*
Note: neither Dose nor Time was significant for any of these variables.								

As can be seen from Table 5 for VOR phase response, the effect of Dose was not significant at any of the forcing functions. The lead and lag of the VOR response changed depending on the forcing function, but there were no fatigue or drug effects. The phase responses for the 0.16 and 0.32 Hz forcing functions clustered together with either little or no lag (-10 degrees per sec), while the 0.04 Hz responses clustered at a lead of about 10 deg/sec and the 0.01 Hz responses clustered at a lead of 35-40 deg/sec. VOR symmetry was also not affected by dose across any of the forcing functions as can be seen in Table 5. Furthermore, it did not appear to be affected by fatigue.

Visual-Vestibular: Optokinetic Response

The Optokinetic Response (OKN) provides a good measure of a person's capability to track moving targets with eyes only. The change in fall-off velocity was not significantly affected by any of the modafinl dosages compared with changes under placebo, as seen in Table 6. Inspecting the means, it can be seen that the greatest reduction in fall-off velocity was under the placebo condition.

Table 6. Summary of Vestibular Testing Functional Results

Test/Variable	Dose	Pre-Drug	Post-Drug	Overall F-Ratios[1]
Visual-Vestibular: Optokinetic Response (OKN)				
Fall-off Velocity (degrees/sec)	0	$\bar{x}$=49.9 SD=15.3	$\bar{x}$=46.9 SD=15.6	Dose: F(2,28)=0.24, *p=0.788* Time: F(1,14)=1.41, *p=0.255* Dose by Time: F(2,28)[2] =0.06, *p=0.906*
	200	$\bar{x}$=50.9 SD=12.7	$\bar{x}$=49.8 SD=14.1	
	400	$\bar{x}$=51.3 SD=9.9	$\bar{x}$=48.7 SD=11.2	
Visual-Vestibular-Somatic (Postural Stability)				
Area of 95% Ellipse Eyes Open (cm^2)	0	$\bar{x}$=4.42 SD=2.72	$\bar{x}$=5.07 SD=3.19	Dose: F(2,26)=0.30, *p=0.746* Time: F(1,13)=6.74, *p=0.022* Dose by Time: F(2,26)=0.03, *p=0.975*
	200	$\bar{x}$=4.18 SD=3.26	$\bar{x}$=4.74 SD=3.70	
	400	$\bar{x}$=4.15 SD=3.24	$\bar{x}$=4.68 SD=3.26	
Area of 95% Ellipse Eyes Closed (cm^2)	0	$\bar{x}$=4.74 SD=2.17	$\bar{x}$=6.18 SD=3.16	Dose: F(2,26)=6.25, *p=0.006* Time: F(1,13)=5.97, *p=0.030* Dose by Time: F(2,26)=1.17, *p=0.325*
	200	$\bar{x}$=4.65 SD=2.27	$\bar{x}$=5.28 SD=3.82	
	400	$\bar{x}$=3.92 SD=2.80	$\bar{x}$=3.75 SD=1.62	

Notes:
1. The F-Ratios for Main Effects are listed when the Dose by Time interaction was not significant.
2. Huynh-Feldt adjustment used when Mauchly's test for sphericity failed.

Visual-Vestibular-Somatic (Postural Stability)

For the area of 95% ellipse (Force Platform area of the ellipse that captured 95% of the center of pressure), the only significant Dose effect was found for the eyes closed condition, Table 6. Post hoc testing found no significant differences among doses with respect to pre- to post-changes. However, inspection of the means showed a pattern similar to previous variables showing degradation in the placebo treatment, with attenuation under modafinil.

Vestibular Findings Unrelated to the Experiment's Hypotheses

Assessing the data for gender effects we found that our sample of females had significantly longer saccade latencies by approximately 15% compared to the males in the sample. In group effects we found that saccade latency was significantly longer for those who

experienced VOR/OKN testing before the saccade test. There appeared to be a lengthening of saccade latency by the VOR/OKN procedure, and the effect appeared to be slightly greater for females (+16%) than for males (+12%). Similar effects were found for the phase response in the Vestibulo-Ocular Response (VOR). The phase response measure lead by approximately 2 degrees when the VOR/OKN testing procedure preceded the visual and postural sway testing compared to when it followed it. None of these group differences appeared to interact with the drug or dose effects and, therefore, were not discussed in this report.

Performance Testing

Although the performance benefits of modafinil are well documented, we wished to show that they were present in this study along with the evaluation of the vestibular system. Furthermore, the potential problem of overconfidence under modafinil was assessed using performance test scores. This section quickly reviews the cognitive performance effects of modafinil and then moves into an evaluation of the overconfidence measures. Cognitive performance tests were given before and after each vestibular testing session and prior to ending the test session at 0530 in the morning. The final cognitive testing session was not analyzed because of possible end of test session effects. The PVT test will be discussed first, followed by the cognitive performance test results, followed by the assessment of overconfidence using participant subjective estimates of performance.

Psychomotor Vigilance Test

The Psychomotor Vigilance Test (PVT) is very sensitive to fatigue and every measure--lapses, mean reciprocal reaction time (MRRT), mean reaction time(MRT), and the standard deviation of reciprocal reaction time (SRRT)-- showed a significant effect of Dose. The means, standard deviations and F-ratios are shown in Appendix A. Once a Dose by Time interaction was found significant for a measure, doses were evaluated by comparing the change between each Trial (2, 3 or 4) and Trial 1 for each modafinil dose with placebo. This method evaluated each dose against placebo while adjusting for any pre-drug differences. Figure 5 shows a plot of lapses across the test trials for each drug dose. The other PVT measures graphed similarly with a significant difference between the placebo dose and the 200 and 400 mg doses on Trial 4 (see Appendix A). All of the measures, except lapses, showed significant changes at Trial 3 as well (see Appendix A). The 200- and 400-mg doses do not appear to be different from each other at either Trial 3 or 4 (a statistical test would be non-orthogonal to the comparisons with placebo).

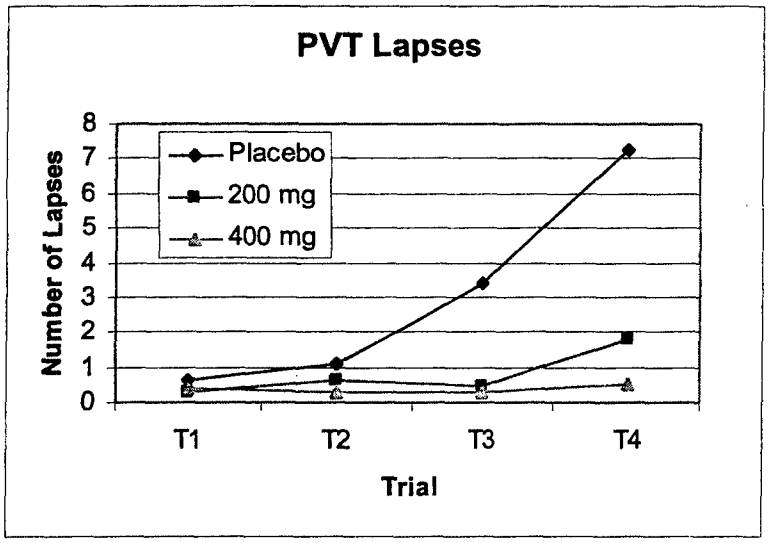

Figure 5. Interactive effects of Dose and Trial on lapses. The 200 and 400 mg doses were significantly different from placebo at Trial 4, but not at Trial 3. The drug treatment was given between Trials 2 and 3.

Two-Choice Response Test

While the PVT assesses the ability to remain vigilant to the onset of a cue over 10 minutes, the Two-Choice Response Test assesses the capability to make a simple decision about a stimulus over a short time period. The means, standard deviations and F-ratios are shown in Appendix A. The same method used to evaluate the PVT data was used to evaluate the Two-Choice Response Test. In this test, there were significant Dose effects on reaction time, but not on accuracy. Reaction time was significantly slower post-drug (early morning) under the Placebo than with the 200- and 400-mg doses, as shown in Figure 6. There were significant changes between Trial 1 and 4 for either modafinil dose compared with Placebo (see Appendix A). The changes between Trial 1 and 3 for the 200 mg dose and Placebo was also significant. The Placebo comparison with the 400 mg dose was close at $p=0.083$. The 200- and 400-mg doses do not appear to be different from each other at either Trial 3 or 4 (a statistical test would be non-orthogonal to the comparisons with placebo).

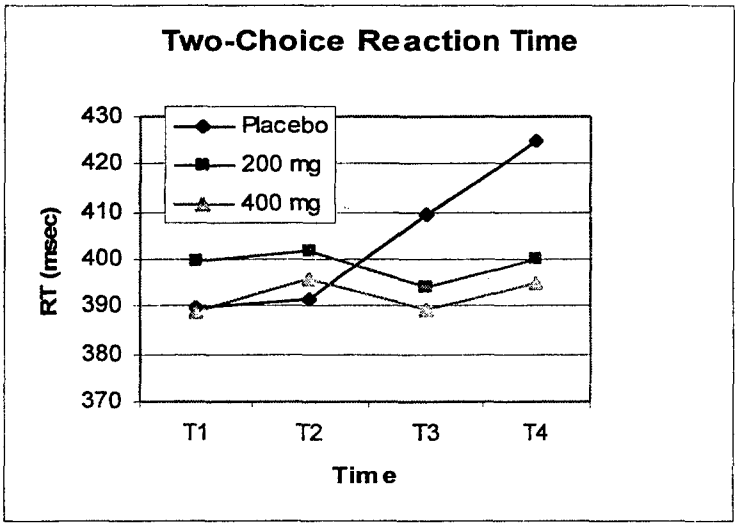

Figure 6. Interactive effects of Dose and Trial on Two-Choice Response time (n=15).

Matching-to-Sample Test

The Matching to Sample test assesses short-term memory for patterns and the ability to mentally rotate the memorial trace for comparison with two alternative patterns. There were significant Dose effects of on both reaction time and accuracy. The means, standard deviations and F-ratios are shown in Appendix A. The same analysis was conducted for this test as for the Two-Choice Response Test. Accuracy dropped over six percent and reaction time was significantly slower post drug (early morning) under the Placebo than with the 200- and 400-mg doses. Accuracy was maintained under modafinil, but not under Placebo, as shown in Figure 7. For accuracy, the changes between Trial 1 and 4 for either modafinil dose compared with Placebo were significant. The change between Trial 1 and Trial 3 was significant between the 200 mg dose and Placebo (the 400 mg dose was close at p=.072). For reaction time compared with Placebo, only the Trial 1 and 4 differences for the modafinil doses were significant, see Appendix A. The 200- and 400-mg doses do not appear to be different from each other at either Trial 3 or 4 (a statistical test would be non-orthogonal to the comparisons with placebo).

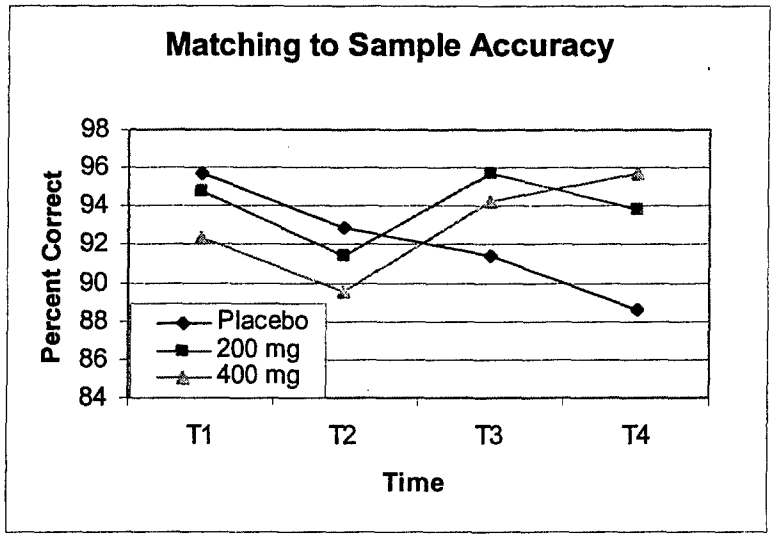

Figure 7. Interactive effects of Dose by Trial on matching to sample accuracy.

Tapping Task

The Tapping Task is a pure motor task that requires a minimum of visual input. It was included since modafinil, possessing the qualities of a stimulant, could push motor performance above the placebo baseline. There was a significant effect of Dose on the mean number of taps in 10 seconds. The means, standard deviations and F-ratios are shown in Appendix A. There were significantly fewer taps post drug (early morning) under the Placebo than with the 200- and 400-mg doses. Tapping was maintained under modafinil, but not under Placebo, as shown in Figure 8. The differences between Placebo and both drug doses were significant comparing the differences from both Trial 1 to 4 and from Trial 1 to 3. The 200- and 400-mg doses do not appear to be different from each other at either Trial 3 or 4 (a statistical test would be non-orthogonal to the comparisons with placebo).

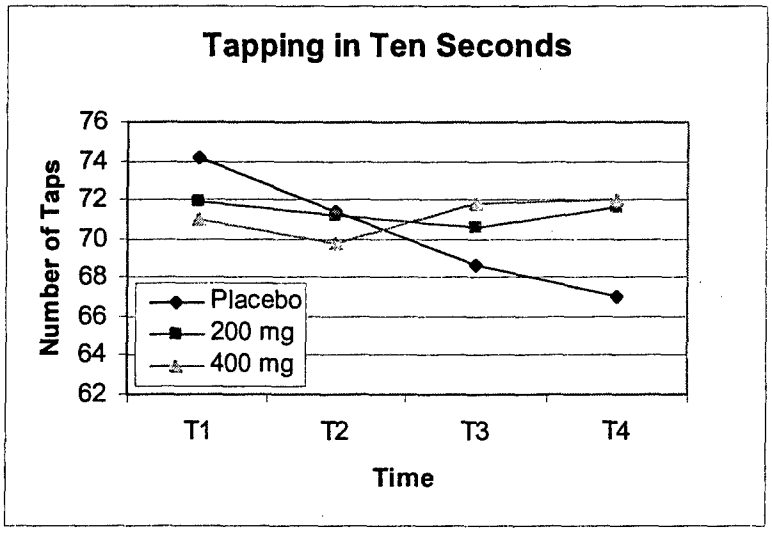

Figure 8. Interactive effects of Dose by Trial on number of taps in 10 seconds.

The PVT and cognitive performance tests showed that performance was maintained under modafinil but declined under placebo consistent with many studies in the literature. The next section explores using a participant's estimate of their performance prior to completing a test as a way to measure overconfidence.

Performance Estimation and Overconfidence

Measures of Overconfidence

It has been suggested that ingestion of modafinil may cause a person to tolerate greater risks to themselves or their mission relative to someone who is fatigued. We hypothesized that this increased risk could result from an individual under a medication such as modafinil believing that their improved alertness would allow them to perform better than was actually possible. To test this notion, our participants were asked to estimate their accuracy and reaction time scores before completing each of the cognitive tests (Two-Choice Test, Match-to-Sample and Tapping). We assessed the differences between their estimates and their actual performance scores under each of the doses at each of the four test times. A significant difference between the predicted and actual performance would be labeled as over-confident if their estimate was better than their actual performance and labeled as underconfident if their estimate was worse. For Accuracy and Tapping, overconfidence would be reflected in significant positive differences, whereas for reaction time, overconfidence would be reflected in significant negative differences.

The overconfidence measures for neither accuracy nor reaction time from the Two-Choice Response Test or the Matching-to-Sample Test revealed any significant Dose by Time effects. The same was true for the number of taps in the Tapping Test. The means, standard deviations and F-ratios are shown in Table 7. Figure 9 shows a plot of the predicted minus the actual scores for all five measures. There were two significant Time effects for the Two-Choice accuracy measure and the number of taps in the Tapping test. The former showed a linear decreasing trend across time reflecting less confidence over time regardless of dose; the latter showed a curvilinear trend with no explanation.

Table 7. Summary of Cognitive Performance Test Results

			Pre-Drug		Post-Drug		
	Dose		**T1**	**T2**	**T3**	**T4**	**Overall F-Ratio[1]**
Two Choice Reaction Time Test – Predicted - Observed							
Accuracy	0	Mean	1.33	0.18	-3.17	-4.33	Dose:
		SD	4.98	3.83	6.21	6.71	$F(2,22)=0.18$, *p=0.839*
	200	Mean	-0.33	-0.17	-2.75	-1.00	Time:
		SD	4.56	2.62	4.54	3.77	$F(3,33)^2=3.48$, *p=0.027*
	400	Mean	0.83	-1.00	-0.83	-2.50	Dose by Time:
		SD	3.59	4.45	2.76	4.46	$F(4,40)^2=1.42$, *p=0.247*
RT	0	Mean	65.9	11.2	42.8	19.7	Dose:
		SD	247.0	57.1	129.6	125.5	$F(1,14)^2=1.94$, *p=0.186*
	200	Mean	78.8	27.0	197.9	41.2	Time:
		SD	185.0	132.5	479.1	119.5	$F(2,16)^2=1.21$, *p=0.315*
	400	Mean	13.6	25.4	0.9	-6.6	Dose by Time:
		SD	157.8	116.9	85.9	57.8	$F(2,17)^2=0.81$, *p=0.443*
Match-to-Sample Test - Predicted - Observed							
Accuracy	0	Mean	0.92	4.39	0.72	-0.26	Dose:
		SD	5.43	9.54	10.88	9.56	$F(2,24)=1.00$, *p=0.382*
	200	Mean	0.44	4.18	-1.15	-3.08	Time:
		SD	6.90	10.41	8.77	12.74	$F(2,20)^2=2.11$.*p=0.152*
	400	Mean	2.05	3.51	1.54	-3.08	Dose by Time:
		SD	7.47	6.98	7.46	8.03	$F(6,72)^2=0.28$, *p=0.945*
RT	0	Mean	-103.9	61.5	-44.9	-147.2	Dose:
		SD	532.8	309.2	456.9	724.5	$F(1,14)^2=0.05$, *p=0.895*
	200	Mean	-17.6	-126.6	-8.0	-55.6	Time:
		SD	316.4	325.8	522.1	367.7	$F(3,30)=0.28$, *p=0.839*
	400	Mean	49.5	9.7	-103.2	-87.6	Dose by Time:
		SD	489.2	931.9	449.1	579.9	$F(3,31)^2=0.57$, *p=0.646*
Tapping Test- Predicted - Observed							
Number of taps	0	Mean	-3.50	2.00	0.00	0.63	Dose:
		SD	2.98	4.69	4.07	2.67	$F(2,14)=0.56$, *p=0.586*
	200	Mean	-2.75	0.63	-0.25	-1.88	Time:
		SD	4.50	4.07	5.01	4.16	$F(3,21)=4.40$, *p=0.015*
	400	Mean	-3.63	-0.38	-0.88	-3.75	Dose by Time:
		SD	6.46	4.00	7.28	9.19	$F(3,24)^2=0.38$, *p=0.795*

Notes:
1. The F-Ratios for Main Effects are included since no Dose by Time interactions were significant.
2. Huynh-Feldt adjustment used when Mauchly's test for sphericity failed.

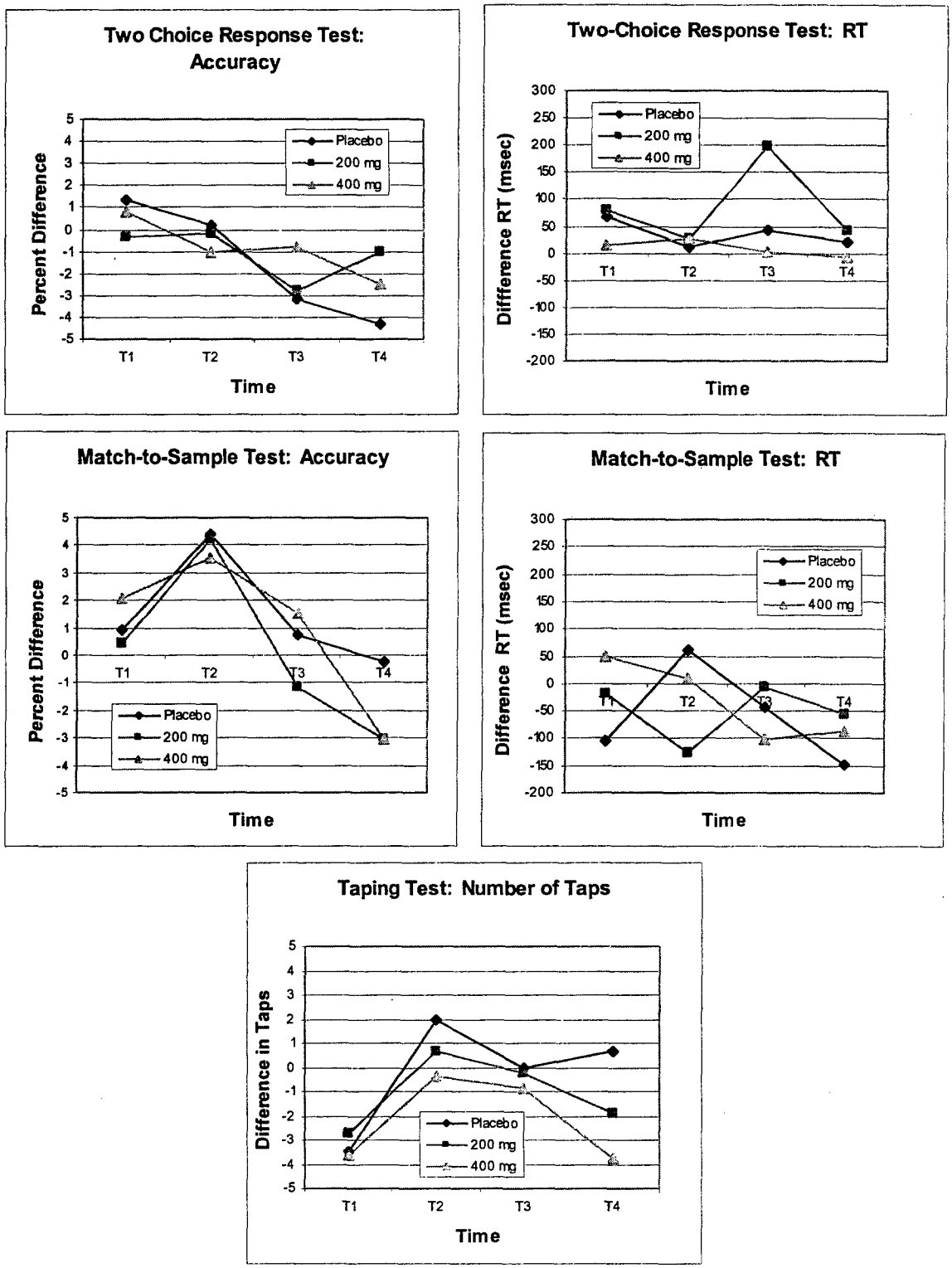

Figure 9. Plots of the difference between predicted and actual performance for each of the five dependent measures.

Another way of viewing these data is shown in Figure 10 for tapping and choice reaction time, where the observed values are plotted against the participant predictions for all drug

conditions combined. Each scatter plot shows a good relationship between participant estimates and actual performance. The reaction time data show a trend toward underconfidence in the placebo condition.

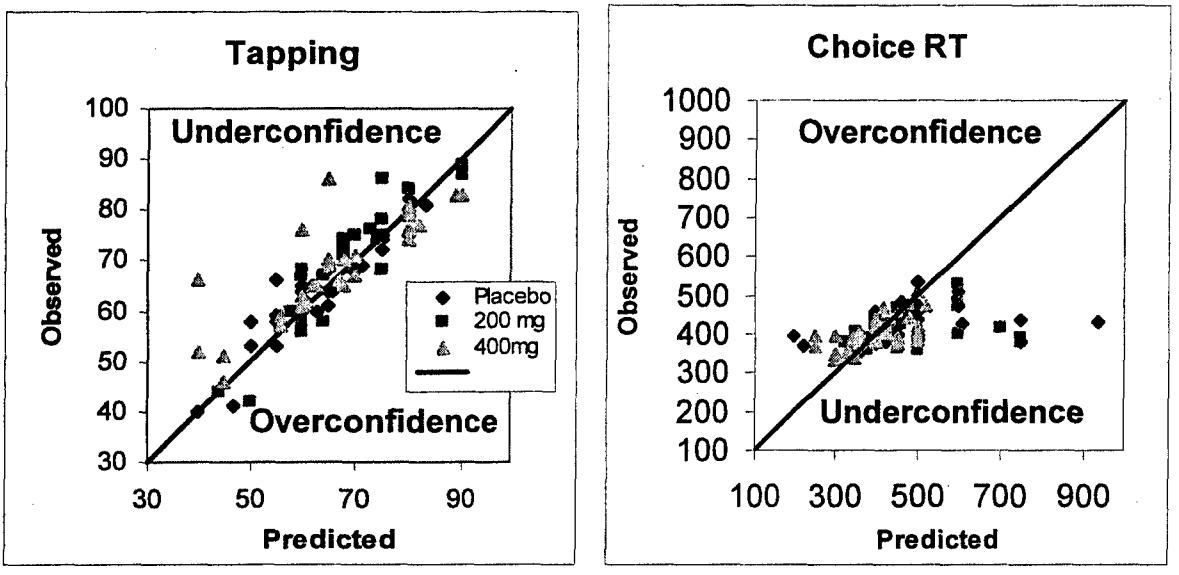

Figure 10. Representative scatter plots of observed performance plotted against participant estimated (predicted) performance.

Subjective Measures

Stanford Sleepiness Scale

Participant responses on the Stanford Sleepiness Scale (SSS) reflect the same pattern of effects shown in the cognitive performance and PVT measures, see Figure 11. The means, standard deviations and F-ratios are shown in Appendix A. The same method used to evaluate the cognitive performance data was used to evaluate SSS. There was a significant Dose effect on sleepiness. Participants reported being significantly sleepier post-drug (early morning) under the Placebo than with the 200- and 400-mg doses. Compared with Placebo, there were significant changes between Trial 1 and 4 and between Trial 1 and 3 for each modafinil dose (see Appendix A). The 200- and 400-mg doses were not different from each other at any Trial.

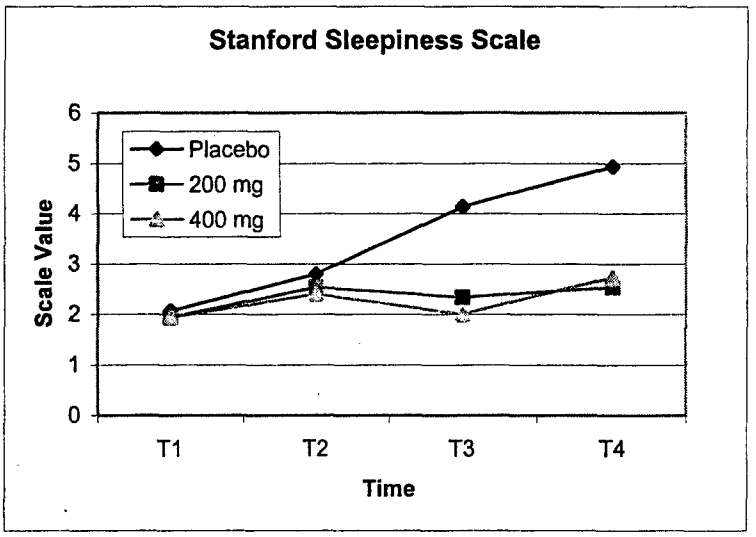

Figure 11. Interactive effects of Dose and Trial on Stanford Sleepiness Scale ratings.

Vestibular Symptom Checklist

The 26 checklist items of Robert Kennedy's Simulator Sickness Questionnaire (Kennedy et al., 1993) were scored according to the instructions resulting in three scales for nausea, oculomotor, and disorientation symptoms. It was assumed that some of the scales would be affected by fatigue, some by the vestibular challenge (rotating chair) and some by modafinil. Because the emphasis of the study was to assess the effect of modafinil on vestibular function and symptoms, the analysis attempted to remove the effect of the rotating chair from the fatigue and modafinil effects. The Trial 1 baseline was prior to the rotating-chair, vestibular testing, so examining the changes in the values from Trial 1 to Trial 3 would remove any potential chair effects from the results. Similarly, examining the change from Trial 2 to 4 assessed the fatigue and modafinil effects holding the chair effects, if any, constant. Changes were evaluated with the Wilcoxon Signed Ranks Tests with alpha = 0.05.

Table 8 presents the changes in the scales from Trial 1 to 3 and Trial 2 to 4 for each of the doses. Using this analysis, the only significant effect was for the oculomotor scale. This scale includes items related to eyestrain, difficulty focusing, blurred vision and headache. The differences are the result of the placebo and 400 mg modafinil doses showing more symptoms as fatigue accumulates during the early morning with the 200 mg modafinil dose appearing to protect against those symptoms. Examination of the symptoms for this scale indicates that modafinil in low doses may protect against them, but higher doses may cause an increase of the symptoms that occur under fatigue. Slight blurred vision was indicated by four participants pre-drug and by one subject under the 400 mg dose. The trend across these three subscales was for the placebo dose to show the greatest increase with the onset of fatigue in the early morning hours.

Table 8. Percentage of participants developing (or increasing) vestibular symptoms after dosing, based on the Simulator Sickness Questionnaire

Vestibular Survey	Trial 1 to 3			Trial 2 to 4		
Subscales	**Placebo**	**200mg**	**400mg**	**Placebo**	**200mg**	**400mg**
Disorientation	11.8	12.5	25.0	58.8	18.8	31.3
Nausea	41.1	31.3	43.8	47.1	31.3	56.3
Oculomotor	88.2	25.0*	62.5	76.5	43.8*	75.0

Notes:
Trial 1 to 3 changes are prior to vestibular testing in the rotator chair; Trial 2 to 4 changes are after the testing.
* significantly different from Placebo and 400mg modafinil (Wilcoxson Signed Rank, $p<0.05$).

Drug Symptom Checklist

To assess the impact of fatigue and dose on symptoms, a Wilcoxon Signed Rank Test was performed on each of the 38 symptoms in the Drug Symptom Checklist. No severe symptoms (greater than 4 on a 7 point scale) were reported. Table 9 shows the percentage of participants whose symptoms increased from their pre-drug baselines (Trials 1 and 2) to post-drug testing (Trials 3 and 4). The testing revealed a greater percentage of participants developing drowsiness during the placebo condition versus the 200- and 400-mg doses. It also revealed a greater percentage of participants developing tingling, dry mouth and nervousness during the 400-mg dose versus the placebo. Although not statistically significant, there is a trend for headaches and nausea to increase under the 400 mg dose of modafinil. Thus, while modafinil (200 and 400 mg) was successful in reducing perceptions of drowsiness, the 400 mg dose induced perceptions of tingling, dry mouth and nervousness. The 200-mg dose appeared to be just as effective as the 400-mg dose in reducing drowsiness, but with fewer adverse side effects.

Table 9. Percentage of participants developing (or increasing) symptoms after dosing, based on the Drug Symptom Checklist.

General Survey		Modafinil	
Symptom	**Placebo**	**200mg**	**400mg**
Headache	0.0	25.0	31.3
Chills	5.9	6.3	31.3
Drowsiness	88.2	18.8*	25.0*
Nausea	11.8	31.3	31.3
Tingling	0.0	18.8	31.3*
Dry mouth	5.9	18.8	37.5*
Nervousness	0.0	18.8	37.5*
Anxiety	0.0	18.8	18.8
Trembling	0.0	0.0	18.8
Sore throat	0.0	0.0	18.8
Increased appetite	5.9	12.5	18.8
Increased flatulence	5.9	12.5	18.8

Notes:
No severe symptoms (scores greater than 4) were reported in this study.
* significantly different from placebo (Wilcoxon Signed Rank Test, $p<.05$).

Other Physiological Measures

Vital signs -- temperature, heart rate and blood pressure -- were analyzed using a repeated measures ANOVA by comparing each of the three doses at each sample time (2030, 2300, 0000, 0130, 0300, 0400, and 0500). Significant effects were followed with simple pair-wise comparisons to determine to locus of the effect. The means, standard deviations and F-ratios are listed in Appendix B.

Oral Temperature

Modafinil is known to affect measures of body temperature (McLellan, Ducharme, Canini, Moroz, Bell, Baranski, Gil, Buguet, and Radomski, 2002) and our experiment was not different. Modafinil significantly increased oral temperature at 0300 and thereafter, approximately three and a half hours after ingestion. The means, standard deviations and F-ratios are listed in Appendix B. The mean increase for 200 mg ranged from 0.4 degrees at 0300 to 0.8 degrees at 0530 and for 400 mg from 0.6 degrees at 0300 to 0.9 degrees at 0530. Figure 12 shows these effects. The oral temperature under placebo and 200 mg dropped 0.7 degrees from 2030 to 0300 hours, whereas under 400 mg dropped only 0.3 degrees. Under placebo the temperature drop widened to 1.1 degrees while the decrease under modafinil was unchanged at 0530 hours.

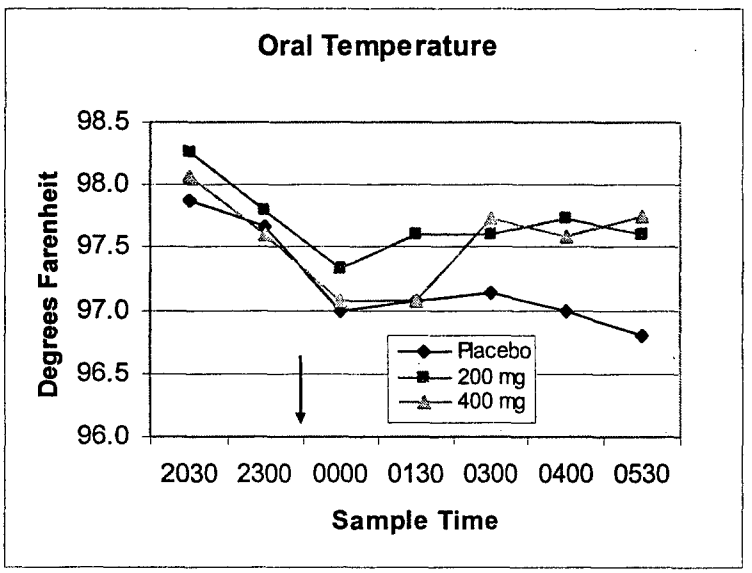

Figure 12. Effect of Dose and Time on oral temperature. Arrow indicates time of dosing.

Heart Rate

One side effect of modafinil is an increase in heart rate, see Figure 13. In this study, heart rate becomes significantly elevated compared to placebo at 0300. The increases continue to the final point of testing at 0530, but they only exceed their baselines at 2030 by 3 BPM for both doses. Over this time period, the placebo condition dropped 3 BPM compared to its baseline.

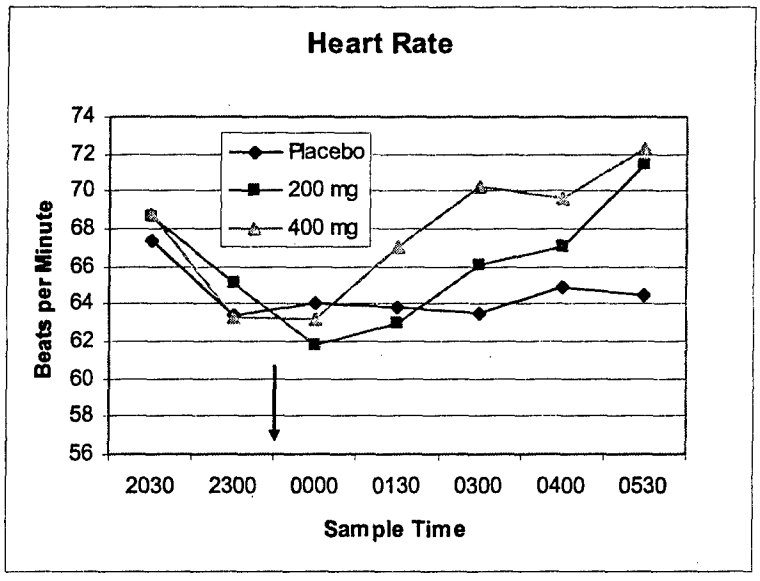

Figure 13. Effect of Dose on heart rate across time. Arrow indicates time of dosing.

Blood Pressure

Modafinil is known to raise blood pressure (Cephalon, 2004) and this study showed similar increases in mean arterial pressure, systolic pressure and diastolic pressure. Figure 14 shows mean arterial pressure. The significant increases for mean arterial pressure began at 0130 for 400 mg, but were only statistically significant for 200 mg starting at 0400. A similar effect was seen for systolic pressure in Figure 15 and diastolic pressure in Figure 16. Under modafinil, these pressures are clearly higher than the baseline pressures at 2030; placebo pressures tend to fluctuate around baseline. Mean arterial pressure was 4-5 mm Hg higher for 400 mg and 200 mg compared to their baselines at 2030. In no case was there a significant difference between 200 and 400 mg of modafinil.

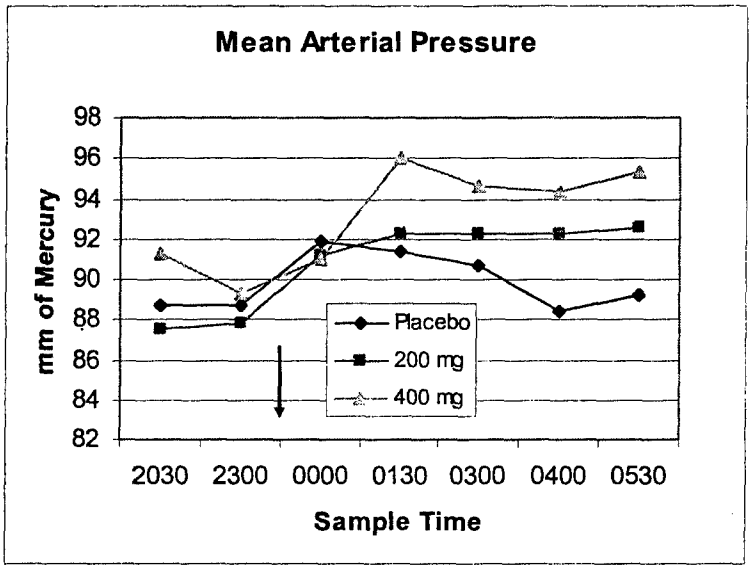

Figure 14. Effect of Dose on mean arterial pressure. Arrow indicates time of dosing.

As shown in Figure 15, systolic pressure at 0530 is 8 mm Hg higher for 400 mg and 7 mm Hg higher for 200 mg compared to their baselines at 2030. For none of the sample times was there a significant difference between 200 and 400 mg of modafinil.

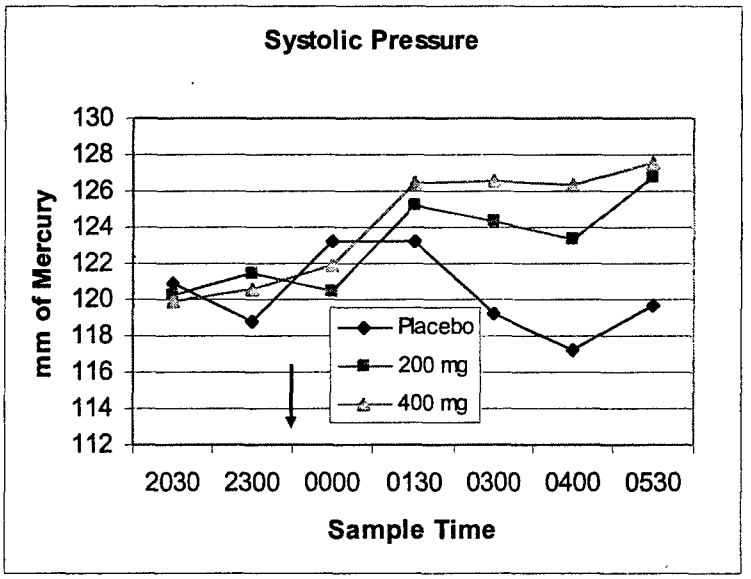

Figure 15. Effect of Dose on systolic pressure across time. Arrow indicates time of dosing.

Diastolic pressure was 5 mm Hg higher for 400 mg and 4 mm Hg higher for 200 mg compared to their baselines at 2300, Figure 16. No sample time for the 200 mg dose was significantly different from placebo. In no case was there a significant difference between 200 and 400 mg of modafinil.

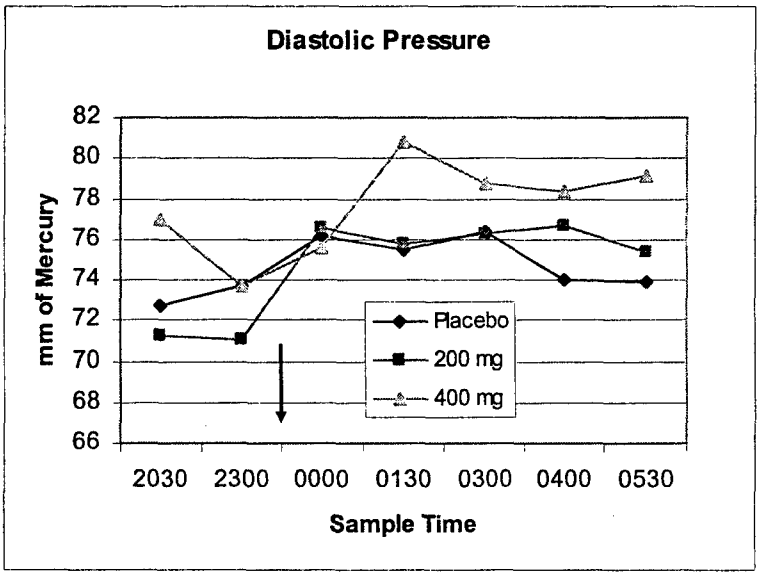

Figure 16. Effect of Dose and Time on diastolic pressure. Arrow indicates time of dosing. Whereas the 2030 value for the 400 mg was influenced by one subject with a high pressure, the 0130 value of 80.8 mm Hg was not.

Fluid Balance

Fluid intake and urination occurred at random times related to participant's motiviation. Since intake and output were recorded for each participant over the 12 hour testing sessions, a measure of fluid balance was computed. Fluid intake was accumulated over the period 2200-0400 and urine output was accumulated from 0000-0600. Since modafinil may decrease fluid balance the values were compared for each dose. The specific gravity of the urine was also assessed. Table 10 contains the means, standard deviations and statistical results for the various doses. Fluid intake for the 400 mg dose was significantly different from the placebo, Figure 17. There was a trend for fluid balance to decrease under modafinil. The concomitant greater urine output then lead to a decrease in specific gravity. When less urine is retained, greater amounts are released causing that which is excreted to be less concentrated.

Table 10. Fluid Intake, Fluid Balance and Specific Gravity by Dose.

Measure		Placebo	200	400	F-Ratios and Contrasts
Intake	$\bar{x}$=	1420	1517	1778	F(2,28)=3.40, *p=0.048* 0 vs 200, SE=129.6, *p=0.467* 0 vs 400, SE=118.1, *p=0.009* 200 vs 400, SE=172.4, *p=0.152*
	SD=	540	603	781	
Fluid Balance	$\bar{x}$=	549	401	319	F(2,28)=2.10, *p=0.141*
	SD=	351	430	320	
Specific Gravity	$\bar{x}$=	1.0221	1.0139	1.0125	F(1,16)[1] =2.22, *p=0.155*
	SD=	0.0228	0.0061	0.0057	
Note: [1] Huynh-Feldt adjustment used when Mauchly's test for sphericity failed.					

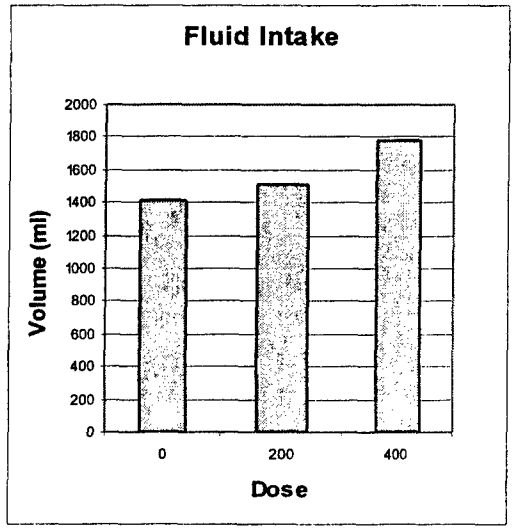

Figure 17. The effect of modafinil on fluid intake.

Urine Assay for Modafinil

The presence of modafinil in the urine of the 15 participants whose data are reported, above, was detected appropriately except in one case: the Week 2, 200-mg dose was not detected in one male subject. The sample was re-analyzed, but with the same result. The Week 3, 400-mg dose was detected at a very low level: the nominal, grand mean assay result for modafinil presence was 13.5 +/- 9.5 mcg/ml across the two wavelengths; this sample produced results of about 1.6 mcg/ml. Apparently, this subject metabolized modafinil rapidly or excreted its metabolites quite slowly. Alternatively, or in addition to this source of error, we collected the non-detection urine sample from this subject sooner after drug ingestion than for the other participants. The samples were collected, generally, at 02:26 +/- 1.10 h. This participant's samples were collected at 01:05 (no detection) and 02:23 (unusually low level detected). The absence of modafinil in the urine of all 15 subjects whose data are reported was appropriately confirmed for the placebo condition.

DISCUSSION

Gaining confidence in the efficacy of modafinil was only a secondary aspect of this vestibular safe-to-fly assessment. Primarily, we were concerned about developing an acceptable degree of confidence in the lack of undesirable vestibular effects that may be caused by modafinil. The generic problem we faced, of course, was trying to prove the negative. There is no safe-to-fly experimental design that one can apply to this concern because a study of this nature cannot be designed under the precepts of the scientific method. We can simply design scientific (that is, systematic and generalizable) investigations that emphasize rejection of the null hypothesis of no difference between treatments.

In this investigation, we established our sample size such that our potential rejection of the null hypothesis for a paired t-test could be made at the 95% level of confidence. In addition, our sample size was large enough to provide a relatively good probability that our acceptance of the null hypothesis was appropriate (the power of our tests was high). Even so, for those cases in which we could not reject the null hypothesis, all we could say was that in this particular design, this particular treatment failed to produce a potentially reliable effect. We cannot generalize our negative result.

Specifically, the primary focus of this study has been to investigate the possible effects of two doses of modafinil on vestibular function, on overconfidence and on urine output. In addition, other effects have been investigated including cognitive performance, temperature, heart rate, blood pressure, subjective simulator sickness and drug symptoms. Each of these is considered in the following section.

"Vestibular" Effects

This assessment of the "vestibular" effects of modafinil was carried out at four levels of central nervous system function: visual, vestibular, visual-vestibular, and visual-vestibular-somatic (Shepherd, 1994; Westmoreland et al., 1994). Both fatigue and modafinil dose effects are discussed here.

Visual: Saccadic Eye Movements. We detected an effect of fatigue on peak and mean saccadic velocities: they were about 7% and 8% slower, respectively, from evening to early morning. We ascribed this time of night effect on saccade velocity to additive fatigue effects of the time of prior wakefulness and the metabolic circadian rhythm. Thus, it appeared that there was an effect of fatigue on saccade velocity that was not ameliorated by modafinil.

Smooth Pursuit Tracking. For smooth pursuit gain, there was a significant effect of modafinil and a significant interaction between modafinil and fatigue. The *post hoc* test indicated that gain was apparently impaired during the early morning hours (Trial 2) with Placebo compared with both the 200- and 400-mg Doses. The gain under the modafinil doses was only slightly higher than pre-drug, evening. Thus, it appeared that this was an effect of fatigue on smooth pursuit gain that was ameliorated by modafinil.

The saccadic component of smooth pursuit eye movements was sensitive to the interaction of modafinil and fatigue. The saccade components of smooth pursuit were reduced by both modafinil doses but increased with fatigue. Thus, it appeared that this was an effect of fatigue on smooth pursuit saccadic component that was also ameliorated by modafinil. Although symmetry was not significant ($p=0.076$) the trend was for the eyes to track more symmetrically under the 400 mg dose than under placebo during the early morning hours.

Visual-Vestibular-Somatic: Postural Stability. In neither the eyes open nor eyes closed conditions of this experiment did we find a significant effect of modafinil on postural sway. However both conditions were sensitive to fatigue. The largest increase was under the placebo condition under both conditions.

There were four "vestibular" measures for which some sort of a Dose effect and/or a fatigue (placebo Trial) effect was not detected: saccade latency, smooth pursuit symmetry, vestibulo-ocular response (VOR, gain, phase response and symmetry), and the optokinetic response (OKN) fall-off velocity. Excepting the OKN measure, we felt reasonably comfortable failing to reject the null hypothesis for the other three measures because of the high power and the absence of any negative trends for modafinil. Unfortunately, OKN was the only measure of visual-vestibular function and the low power of the OKN measurement technique continues to be of concern. Inspecting the means in Table 7, it can be seen that the greatest reduction in fall-off velocity was under the placebo condition, implying that performance under modafinil may actually improve the OKN response. Our findings trend in the same direction as the findings of Collins W. E., 1988, who found a decline in OKN with fatigue. He found the fall-off velocity was 60 – 70°/sec when rested and 30°/sec when fatigued. Our participants ranged between 47 and 51°/sec. Compared to his findings, we saw a lower than expected fall-off velocity for the rested state, 49.9 °/sec, and a higher than expected fall-off velocity for the fatigued state, 46.9 °/sec. Our failure to find much change in fall-off velocity is not surprising in that our participants were deprived of sleep for only about 21 hours whereas those in Collins' study were deprived for approximately 50 hours.

To summarize these differential fatigue and dose effects on vestibular function:

- At the visual level of assessment there were mixed effects. There appeared to be a depressant effect of fatigue on saccade velocity that was not ameliorated by modafinil.
- There appeared to be a depressant effect of fatigue on smooth visual pursuit gain that was ameliorated by modafinil. Additionally, a greater saccadic component was needed to track smoothly under fatigue that was also ameliorated by modafinil.
- At the visual-vestibular-somatic level of assessment, fatigue caused increased postural sway that was not significantly ameliorated by modafinil.

Caldwell (1999) suggested that the interactive effects of fatigue, motion and modafinil may cause dizziness in pilots. This experiment attempted to reproduce that effect with a sophisticated examination of the functionality of the intact vestibular system concentrating on the lateral or horizontal semicircular canal's responsiveness to rotation in non-pilot subjects. The experimental manipulations did not investigate motion related to the other semi-circular canals. Under the conditions tested, rotational motion (yaw), no adverse effects of modafinil were uncovered. Interestingly, the visual system, as measured by saccade velocity and smooth pursuit tracking, appeared to benefit from modafinil doses of 200 and 400 mg compared to placebo.

Holmes, Arrowsmith and Turner (2001) presented a paper at the 36th UK Group Conference on Human Response to Vibration, held at QinetiQ Ltd, Farnborough, UK, on the effects of modafinil and sleep deprivation on susceptibility to motion sickness that investigates vestibular responses in a creative way. She too was responding to Caldwell et al. (1999) reporting symptoms of nausea in subjects on modafinil during and after a flight simulator task during a sleep deprivation experiment. The objective of her experiment was to investigate the effects of modafinil on susceptibility to motion sickness, using a gold standard clinical test. A secondary aim was to investigate the effects of time of day and sleep deprivation on motion sickness thresholds. Twelve subjects (6M, 6F) participated in 3 counter-balanced experimental conditions (placebo, 200mg and 300 mg) during the circadian nadir (02:00 – 06:00, 19-21 hrs sleep loss) one week apart. Motion sickness susceptibility was determined by the time taken to report moderate nausea during exposure to a cross-coupled motion stimulus. They found no effect of modafinil on susceptibility to motion sickness. They attributed their conflicting results to the lower dose of modafinil, the shorter duration of sleep loss or the type of motion stimulus used, relative to the Caldwell study.

Also relevant here are the results from the participant responses to the Simulator Sickness Survey, Table 9. There were no significant effects for any of the doses on the Disorientation and Nausea subscales. The one significant finding showed 200 mg of modafinil to reduce the oculomotor symptoms from fatigue better then placebo. Since the 400 mg dose fell between placebo and the 200 mg dose, it would be easy to speculate that the 200 mg dose is optimal. We chose to conclude that modafinil does not affect simulator sickness symptoms at the doses administered and regardless of the vestibular challenge resulting from testing. Since this study tested a 400 mg dose of modafinil, the study casts doubt on the hypothesis that the pilot's reports of dizziness were due to the relatively high dose used in Caldwell's study. Caldwell's last assertion that his reported effects might have been attributable to the motion of the flight simulator coupled with computer-based scenery models remains the best

explanation of his finding. Although the interaction of those effects with modafinil have not been ruled out and further research is needed to isolate this finding.

Cognitive Performance and Overconfidence

Both Baranski and Pigeau (1997) and Batéjat and Lagarde (1999) found that modafinil produced overconfidence effects in their studies 2-4 hours after ingestion. After the collection of data in the present study, Baranski, Gil, McLellan, Moroz, Bugnet and Radomski (2002), published another study of modafinil and concluded that "subjects displayed evidence of good self-monitoring on the modafinil trial."

The present study assessed cognitive performance, vigilance and subjective sleepiness demonstrating the typical findings regarding fatigue and modafinil effects on three cognitive performance tests, PVT and the Stanford Sleepiness Scale. Sleep loss and circadian disruption degraded performance in all three categories under the placebo treatment and both doses of modafinil maintained performance and vigilance while reducing sleepiness and drowsiness similar to baseline levels (Figures 7-10, Figure 13 and Appendix A).

The experimental procedures of the present study for assessing overconfidence expanded on those of Baranski by not only requiring participants to estimate their anticipated accuracy, but also their anticipated reaction time in two of the three performance tests. Compared to Baranski, the reaction time and tapping measures of this study provide somewhat better estimates of predicted and actual performance that are free of potential ceiling effects. In addition, the Tapping task provided a simple motor task that might be sensitive to a participant's possible perceptions of heightened motor capability under modafinil. Confidence was calculated by using the difference between estimated and observed performance. For accuracy and tapping, positive differences denoted "overconfidence" and negative differences denoted "underconfidence." For reaction-time, the reverse was true. ANOVA and individual comparisons of participant estimated and actual performance under the three drug conditions at baseline and post drug revealed no consistent significant differences. We detected no overconfidence as a result of dose or fatigue for Two-Choice Reaction Time accuracy or reaction-time, for Match-to-Sample accuracy or reaction-time or for number of taps (Tapping). Similar to Baranski, et al. (2002) under fatigue, we saw slight underconfidence in Two-Choice Reaction Time accuracy but this was unrelated to dose.

Baranski proposes three possible explanations for the different findings in his two studies.

1. His first study used a between-subjects design whereas his second used a within-subject design.
2. The 1997 study involved a continuous work paradigm whereas the 2000 study required self-monitoring assessments at 6-hr intervals.
3. Baranski and Pigeau (1997) administered a single dose of 300 mg of modafinil to participants who were previously sleep deprived, but in the 2000 study, three, 100 mg doses were given over each 24 hour period.

He concluded that modafinil per se does not affect one's self-monitoring ability, but that large (300 mg), single doses may have unwanted side effects (Baranski et al, 2002). Since

the present study was a within-subjects design similar to Baranski's second study, it cannot provide direct information to the first difference. Baranski suggests that the within-subject design may permit a clearer reference point for self-monitoring. Other things being equal, this assertion could reduce to the participants in a within-subject design merely receiving more practice in estimating performance levels. Examining percent correct measure in the two tasks common to both of Baranski's studies, reveals that his participants initially performed at lower levels going into the 1997 study compared with the 2000 study. This was especially obvious in the addition task (32-53% versus 88%). More importantly, participants in the 1997 study initially underestimated their performance (this difference was statistically significant in the addition task), which implies poor understanding ("calibration") of their performance level. A weak test of this hypothesis (less practiced participants would overestimate their performance under modafinil) would be to examine differences (predicted minus actual) early versus late in testing for the 400 mg dose in the present study. Plots of our data and statistical analyses show no differences for participants receiving the 400 mg dose in their first test session versus participants receiving the 400 mg dose in their third test session. This implies that the participant's ability to estimate their performance did not improve with practice. This provides very weak evidence that the design difference between Baranski's studies (between- versus within-subject) did not contribute to the conflicting findings.

Regarding Baranski's second possible explanation for conflicting results, continuous versus distributed work, the present study used a continuous testing paradigm over 24 hours as opposed to continuous testing over 64 hours in his first study. In our study, evening tests were separated by two hours, as were the morning tests, and the first morning test followed the last evening test by four hours. However, participants were required to work continuously on tasks throughout the 24-hour testing period except for a 45-minute break 2315-0000. Unfortunately our findings cannot eliminate the difference of continuous versus distributed work as a cause of overconfidence in the 1997 study because our study did not continue into the next day where Baranski and Pigeau (1997) found their overconfidence effects.

Baranski's third explanation of the conflicting results really involves two conceptual differences. In the first concept, the first study used single 300 mg doses versus multiple 100 mg doses in the second. In the second concept, the first study timed administration to either be prophylactic, restorative (after fatigue had set in), or prior to sleep. The second study gave modafinil prophylactically similar to clinical usage. The present study can provide additional data on the first difference since our results indicated no overconfidence using single doses of either 200 or 400 mg of modafinil. However, it should be noted again that Baranski and Pigeau (1997) found their overconfidence effects well into the second half-life of the drug, approximately 12-hours after administration for the Perceptual Comparison Task and 14-hours post drug in the Addition Task.

Baranski's final possible explanation for the conflicting results between his two studies reduces to prophylactic versus non-prophylactic administration. This is a very important issue and should be addressed by new research. It is the AF's position that stimulants be administered prophylactically. However, it may be necessary to warn users that delayed

ingestion could lead to over-estimation of performance capability and overconfidence if this outcome is supported in future research.

Fluid Balance

Although an investigation of fluid balance was one of the stated objectives of the study, the restricted time period of the study reduced the reliability of these data. There was a significant intake of fluid, 358 ml, that makes interpretation difficult. Although not significant, there was a trend for the 400 mg condition to reduce the fluid balance relative to placebo, but his may be a diuretic effect or the result of increased cardiac output. The elevated heart rate and blood pressure (MAP, systolic and diastolic) for the 400 mg modafinil dose support the hypothesis of increased cardiac output as the etiology of the trend.

Other Measures

Based on the Drug Symptom Checklist ratings, drowsiness was reduced under the 200- and 400-mg doses of modafinil. However, the 400-mg dose induced dry mouth, tingling and nervousness. Nausea approached significance and should also be included in side effects. Symptoms under the 200-mg dose were rated less frequently and at a lesser severity than symptoms under the 400-mg dose. The 200-mg dose of modafinil seems to moderate fatigue with fewer side effects than the 400-mg dose.

CONCLUSIONS

The findings of this study suggest that modafinil, at the doses tested, is an effective alerting compound that can be used in operational settings without fear of adverse effects stronger than headache, dry mouth, tingling, nervousness, and possibly some mild nausea. When taken prophylactically, modafinil (200 or 400 mg) produced neither vestibular nor overconfidence effects 2-4 hours after administration compared to placebo.

RECOMMENDATIONS

For operations requiring a night of sleep-loss, a single dose of modafinil of either 200 or 400 mg is an effective alerting substance. While neither dose showed particularly harmful side effects, the 200 mg dose was just as efficacious as the 400mg dose, while showing symptoms equal to or better than placebo.

In combination with the Holmes et al. (2001) findings, we recommend that at least one additional scientific investigation of vestibular function under modafinil be conducted to support a safe-to-fly decision about modafinil. Since the present study did not challenge all components of the vestibular system, an additional study involving motion in the other vestibular planes, preferably simulator motion, should examine these doses of modafinil. Once several investigations of acceptable statistical power fail to detect an undesirable effect

of modafinil on vestibular function, then confidence will be increased that the undesirable effect is absent.

More research is needed regarding possible overconfidence effects when modafinil is administered after fatigue has degraded performance. To date, this latter possibility has yet to be ruled out.

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Appendix A

Data and Results for Psychomotor Vigilance Test, Cognitive Performance Tests and Stanford Sleepiness Scale

Psychomotor Vigilance Test (PVT)

			Pre-Drug		Post-Drug		
	Dose		**T1**	**T2**	**T3**	**T4**	**F-Ratios[1] and Contrasts[2]**
Lapses	0	Mean	0.62	1.08	3.38	7.23	Dose by Time: $F(2,29)^3$ =3.23, p=0.047
		SD	0.87	1.50	7.46	8.03	For 0 versus 200 mg:
	200	Mean	0.31	0.62	0.46	1.77	$F(1,12)_{T1T3Chg}$ =1.99, p=0.183
		SD	0.63	1.04	0.88	4.38	$F(1,12)_{T1T4Chg}$ =5.22, p=0.041
	400	Mean	0.38	0.31	0.31	0.54	For 0 versus 400 mg:
		SD	0.96	0.63	0.63	0.78	$F(1,12)_{T1T3Chg}$ =1.77, p=0.208
							$F(1,12)_{T1T4Chg}$ =7.43, p=0.018
Mean Reciprocal Reaction Time (MRRT)	0	Mean	4.63	4.42	4.07	3.67	Dose by Time: $F(4,42)^3$ =13.77, p=0.000
		SD	0.56	0.49	0.66	0.71	For 0 versus 200 mg:
	200	Mean	4.54	4.47	4.44	4.44	$F(1,12)_{T1T3Chg}$ =17.64, p=0.001
		SD	0.56	0.60	0.56	0.61	$F(1,12)_{T1T4Chg}$ =16.90, p=0.001
	400	Mean	4.54	4.44	4.44	4.49	For 0 versus 400 mg:
		SD	0.44	0.46	0.45	0.47	$F(1,12)_{T1T3Chg}$ =22.84, p=0.000
							$F(1,12)_{T1T4Chg}$ =35.87, p=0.000
Mean Reaction Time (MRT)	0	Mean	226.1	238.5	279.9	336.8	Dose by Time: $F(2,26)^3$ =5.97, p=0.006
		SD	29.8	32.1	97.9	116.5	For 0 versus 200 mg:
	200	Mean	230.3	237.3	236.9	244.0	$F(1,12)_{T1T3Chg}$ =5.20, p=0.042
		SD	28.7	36.0	31.9	56.3	$F(1,12)_{T1T4Chg}$ =8.28, p=0.014
	400	Mean	229.4	235.0	234.8	234.0	For 0 versus 400 mg:
		SD	24.2	26.5	23.4	25.4	$F(1,12)_{T1T3Chg}$ =4.81, p=0.049
							$F(1,12)_{T1T4Chg}$ =11.64, p=0.005
Standard Deviation of Reciprocal Reaction Time (SRRT)	0	Mean	3.27	2.96	2.60	1.97	Dose by Time: $F(4,54)^3$ =7.69, p=0.000
		SD	0.59	0.54	0.86	0.97	For 0 versus 200 mg:
	200	Mean	3.15	3.04	3.05	3.00	$F(1,12)_{T1T3Chg}$ =7.50, p=0.018
		SD	0.50	0.57	0.53	0.75	$F(1,12)_{T1T4Chg}$ =14.59, p=0.002
	400	Mean	3.26	3.11	3.12	3.11	For 0 versus 400 mg:
		SD	0.53	0.49	0.46	0.58	$F(1,12)_{T1T3Chg}$ =6.68, p=0.024
							$F(1,12)_{T1T4Chg}$ =14.29, p=0.003

Notes:

1. The F-Ratios for Main Effects have been omitted since the Dose by Time interaction was significant for every measure.
2. The F-Ratios with df=1 represent comparisons of the pre-to-post change under placebo with the pre-to-post change under each modafinil dose.
3. Huynh-Feldt adjustment used when Mauchly's test for sphericity failed.

			Pre-Drug		Post-Drug		
	Dose		T1	T2	T3	T4	F-Ratio[1] & Contrasts[2]
Two Choice Reaction Time Test							
Accuracy	0	Mean	95.73	95.59	96.00	96.00	Dose: F(2,28)=1.11, p=0.342
		SD	3.99	3.41	2.14	3.12	Time: F(3,42)=0.28, p=0.838
	200	Mean	96.53	96.27	97.33	96.40	Dose by Time: $F(4,59)^3$ =0.53, p=0.722
		SD	3.07	2.71	3.35	3.22	
	400	Mean	96.67	96.27	96.40	97.20	
		SD	2.58	2.60	2.29	1.97	
Reaction Time	0	Mean	389.7	391.5	409.6	424.8	Dose by Time: $F(5,69)^3$ =5.25, p=0.000
		SD	34.3	41.6	36.8	38.8	For 0 versus 200 mg:
	200	Mean	399.6	401.5	393.8	400.1	$F(1,14)_{T1T3Chg}$ =11.96, p=0.004
		SD	34.2	33.7	30.8	36.6	$F(1,14)_{T1T4Chg}$ =27.35, p=0.000
	400	Mean	388.9	395.7	389.2	394.8	For 0 versus 400 mg:
		SD	24.8	31.8	23.4	34.0	$F(1,14)_{T1T3Chg}$ =3.48, p=0.083
							$F(1,14)_{T1T4Chg}$ =7.12, p=0.018
Match-to-Sample Test							
Accuracy	0	Mean	95.71	92.86	91.43	88.57	Dose by Time: F(6,78,)=2.78, p=0.017
		SD	4.22	9.23	9.93	7.59	For 0 versus 200 mg:
	200	Mean	94.76	91.43	95.71	93.81	$F(1,13)_{T1T3Chg}$ =5.52, p=0.035
		SD	7.01	9.22	9.28	8.04	$F(1,13)_{T1T4Chg}$ =7.50, p=0.017
	400	Mean	92.38	89.52	94.29	95.71	For 0 versus 400 mg:
		SD	7.33	7.26	8.21	5.61	$F(1,13)_{T1T3Chg}$ =3.83, p=0.072
							$F(1,13)_{T1T4Chg}$ =16.38, p=0.001
Reaction Time	0	Mean	1132	1159	1290	1404	Dose by Time: $F(3,40)^3$ =2.68, p=0.059
		SD	452	472	463	537	For 0 versus 200 mg:
	200	Mean	1144	1240	1162	1183	$F(1,13)_{T1T3Chg}$ =3.12, p=0.101
		SD	361	358	443	361	$F(1,13)_{T1T4Chg}$ =13.41, p=0.003
	400	Mean	1111	1258	1186	1191	For 0 versus 400 mg:
		SD	336	385	492	546	$F(1,13)_{T1T3Chg}$ =0.93, p=0.352
							$F(1,13)_{T1T4Chg}$ =4.46, p=0.055
Tapping Test							
Number of taps	0	Mean	74.20	71.40	68.60	67.00	Dose by Time: F(6,54)=3.35, p=0.025
		SD	9.32	9.48	9.22	9.64	For 0 versus 200 mg:
	200	Mean	71.90	71.20	70.60	71.60	$F(1,9)_{T1T3Chg}$=4.92, p=0.054
		SD	9.01	10.26	9.69	11.13	$F(1,9)_{T1T4Chg}$=13.19, p=0.005
	400	Mean	71.00	69.80	71.80	72.00	For 0 versus 400 mg:
		SD	12.39	12.44	8.31	11.03	$F(1,9)_{T1T3Chg}$=6.75, p=0.029
							$F(1,9)_{T1T4Chg}$=9.70, p=0.012

Notes:
1. The F-Ratios for Main Effects are included when the Dose by Time interaction was not significant.
2. The F-Ratios with df=1 represent comparisons of the pre-to-post change under placebo with the pre-to-post change under each modafinil dose.
3. Huynh-Feldt adjustment used when Mauchly's test for sphericity failed.

Stanford Sleepiness Scale							
			Pre-Drug		**Post-Drug**		
	Dose		**T1**	**T2**	**T3**	**T4**	**F-Ratio & Contrasts**
Scale Value	0	Mean	2.07	2.80	4.13	4.93	Drug by Time: $F(6,84)=12.51$, $p=0.000$
		SD	0.96	0.86	1.06	0.96	For 0 versus 200 mg:
	200	Mean	1.93	2.53	2.33	2.53	$F(1,14)_{T1T3Chg}=21.3$, $p=0.000$
		SD	1.10	1.36	1.23	1.19	$F(1,14)_{T1T4Chg}=29.2$, $p=0.000$
	400	Mean	1.93	2.40	2.00	2.73	For 0 versus 400 mg:
		SD	0.88	0.99	1.07	1.16	$F(1,14)_{T1T3Chg}=30.0$, $p=0.000$
							$F(1,14)_{T1T4Chg}=47.4$, $p=0.000$

Note:
The F-Ratios with df=1 represent comparisons of the pre-to-post change under placebo with the pre-to-post change under each modafinil dose.

Appendix B

Summary of Vital Statistics

Time		Drug Condition			Overall F-Ratio[1], Contrasts[2]
		Placebo	200	400	
Temperature					
2030	Mean	97.9	98.3	98.1	F=(2,28)=4.065, *p=0.028* 0 vs 200, SE=0.163, *p=0.028* 0 vs 400, SE=0.107, *p=0.082* 200 vs 400, SE=0.145, *p=0.189*
	SD	0.64	0.70	0.59	
2300	Mean	97.7	97.8	97.6	F=(2,28)=0.521, *p=0.599*
	SD	0.90	0.77	0.83	
0000	Mean	97.0	97.3	97.1	F=(2,21)=0.951, *p=0.379*
	SD	0.85	0.90	0.80	
0130	Mean	97.1	97.6	97.1	F=(2,28)=3.189, *p=0.057*
	SD	0.80	0.99	0.59	
0300	Mean	97.1	97.6	97.7	F=(2,28)=4.222, *p=0.025* 0 vs 200, SE=0.257, *p=0.094* 0 vs 400, SE=0.163, *p=0.003* 200 vs 400, SE=0.218, *p=0.538*
	SD	0.74	0.64	0.80	
0400	Mean	97.0	97.7	97.6	F=(2,28)=4.570, *p=0.019* 0 vs 200, SE=0.300, *p=0.028* 0 vs 400, SE=0.264, *p=0.045* 200 vs 400, SE=0.191, *p=0.436*
	SD	0.93	0.80	0.91	
0530	Mean	96.8	97.6	97.7	F=(2,28)=25.574, *p=0.000* 0 vs 200, SE=0.175, *p=0.000* 0 vs 400, SE=0.112, *p=0.000* 200 vs 400, SE=0.133, *p=0.295*
	SD	0.94	0.83	0.73	
Heart Rate					
2030	Mean	67.3	68.6	68.8	F=(2,28)=0.267, *p=0.768*
	SD	11.77	10.66	10.38	
2300	Mean	63.4	65.1	63.3	F=(2,28)=0.810, *p=0.455*
	SD	10.47	9.88	14.93	
0000	Mean	64.0	61.8	63.1	F=(2,28)=0.845, *p=0.440*
	SD	10.66	11.10	12.78	
0130	Mean	63.9	63.0	67.0	F=(2,28)=1.541, *p=0.232*
	SD	8.33	8.75	11.10	
0300	Mean	63.5	66.03	70.2	F=(2,28)=8.520, *p=0.001* 0 vs 200, SE=1.699, *p=0.164* 0 vs 400, SE=1.166, *p=0.000* 200 vs 400, SE=1.935, *p=0.049*
	SD	8.18	7.82	9.24	
0400	Mean	64.9	67.1	69.6	F=(2,22)=3.812, *p=0.048* 0 vs 200, SE=1.187, *p=0.094* 0 vs 400, SE=1.652, *p=0.013* 200 vs 400, SE=2.130, *p=0.250*
	SD	8.45	8.89	11.35	
0530	Mean	64.5	71.5	72.3	F=(2,28)=11.068, *p=0.000* 0 vs 200, SE=1.944, *p=0.003* 0 vs 400, SE=2.009, *p=0.002* 200 vs 400, SE=1.470, *p=0.596*
	SD	10.51	10.51	11.17	

Mean Arterial Pressure (MAP)					
Time		**Drug Condition**			**Overall F-Ratio[1], Contrasts[2]**
		Placebo	**200**	**400**	
2030	Mean	88.8	87.5	91.3	F=(1,19)=0.813, *p=0.412*
	SD	8.30	8.14	11.50	
2300	Mean	88.7	87.9	89.3	F=(2,28)=0.336, *p=0.717*
	SD	9.39	9.95	7.95	
0000	Mean	91.9	91.2	91.0	F=(2,28)=0.108, *p=0.898*
	SD	8.80	6.36	8.19	
0130	Mean	91.4	92.3	96.0	F=(2,28)=3.236, *p=0.054*
	SD	9.85	9.46	9.17	
0300	Mean	90.7	92.3	94.7	F=(1,21)=3.043, *p=0.082*
	SD	8.84	6.62	9.78	
0400	Mean	88.4	92.2	94.3	F=(2,28)=8.492, *p=0.001* 0 vs 200, SE=1.517, *p=0.025* 0 vs 400, SE=1.531, *p=0.002* 200 vs 400, SE=1.296, *p=0.130*
	SD	8.67	7.85	9.13	
0530	Mean	89.2	92.5	95.3	F=(2,28)=5.855, *p=0.008* 0 vs 200, SE=1.890, *p=0.098* 0 vs 400, SE=1.383, *p=0.001* 200 vs 400, SE=2.050, *p=0.195*
	SD	9.26	9.64	8.60	
Systolic					
2030	Mean	120.9	120.2	119.9	F=(2,28)=0.107, *p=0.899*
	SD	11.68	10.51	11.15	
2300	Mean	118.7	121.5	120.5	F=(2,28)=0.686, *p=0.512*
	SD	10.81	12.33	11.49	
0000	Mean	123.2	120.5	121.9	F=(2,28)=0.315, *p=0.732*
	SD	11.64	7.64	13.43	
0130	Mean	123.2	125.3	126.4	F=(2,28)=0.586, *p=0.563*
	SD	14.19	12.57	11.27	
0300	Mean	119.2	124.4	126.5	F=(2,28)=3.834, *p=0.034* 0 vs 200, SE=2.351, *p=0.045* 0 vs 400, SE=2.958, *p=0.027* 200 vs 400, SE=2.819, *p=0.456*
	SD	11.54	8.63	14.50	
0400	Mean	117.3	123.3	126.3	F=(2,28)=8.366, *p=0.001* 0 vs 200, SE=1.814, *p=0.005* 0 vs 400, SE=2.425, *p=0.002* 200 vs 400, SE=2.464, *p=0.247*
	SD	11.31	10.55	11.70	
0530	Mean	119.7	126.8	127.6	F=(1,19)=10.365, *p=0.002* 0 vs 200, SE=1.154, *p=0.000* 0 vs 400, SE=2.452, *p=0.006* 200 vs 400, SE=1.922, *p=0.685*
	SD	13.41	11.79	11.18	

Diastolic					
Time		**Drug Condition**			**Overall F-Ratio[1], Contrasts[2]**
		Placebo	**200**	**400**	
2030	Mean	72.7	71.2	76.9	F=(1,18)=1.303, *p=0.280*
	SD	9.15	7.65	14.29	
2300	Mean	73.7	71.1	73.7	F=(2,28)=1.304, *p=0.287*
	SD	9.68	9.60	7.14	
0000	Mean	76.2	76.6	75.6	F=(2,28)=0.158, *p=0.855*
	SD	9.25	7.22	6.39	
0130	Mean	75.5	75.8	80.8	F=(2,28)=3.934, *p=0.031* 0 vs 200, SE=2.181, *p=0.881* 0 vs 400, SE=1.600, *p=0.005* 200 vs 400, SE=2.509, *p=0.066*
	SD	8.75	9.25	9.47	
0300	Mean	76.4	76.3	78.7	F=(2,28)=1.709, *p=0.199*
	SD	8.30	7.75	8.23	
0400	Mean	74.0	76.7	78.3	F=(2,28)=3.219, *p=0.055*
	SD	8.94	7.70	9.79	
0530	Mean	73.9	75.4	79.2	F=(2,28)=2.836, *p=0.076*
	SD	8.51	10.32	8.92	

Notes:
1. The F-Ratios comparing doses at each time.
2. The F-Ratios with df=1, represent a test of the difference between the Doses indicated. $F=t^2$
3. Huynh-Feldt adjustment used when Mauchly's test for sphericity failed.

Appendix C

Symptom Checklist

Please circle the appropriate rating to each of the symptoms listed below that you are experiencing at the time you complete this checklist.

		None		Slight		Moderate			Severe
1	Headache	0	1	2	3	4	5	6	7
2	Neck Pain	0	1	2	3	4	5	6	7
3	Chills	0	1	2	3	4	5	6	7
4	Loss of Balance	0	1	2	3	4	5	6	7
5	Drowsiness	0	1	2	3	4	5	6	7
6	Nausea	0	1	2	3	4	5	6	7
7	Faintness	0	1	2	3	4	5	6	7
8	Numbness	0	1	2	3	4	5	6	7
9	Tingling	0	1	2	3	4	5	6	7
10	Sweating	0	1	2	3	4	5	6	7
11	Chest Pain	0	1	2	3	4	5	6	7
12	Diarrhea	0	1	2	3	4	5	6	7
13	Dry Mouth	0	1	2	3	4	5	6	7
14	Back Pain	0	1	2	3	4	5	6	7
15	Rash	0	1	2	3	4	5	6	7
16	Itching	0	1	2	3	4	5	6	7
17	Swelling	0	1	2	3	4	5	6	7
18	Nervousness	0	1	2	3	4	5	6	7
19	Dizziness	0	1	2	3	4	5	6	7
20	Anxiety	0	1	2	3	4	5	6	7
21	Confusion	0	1	2	3	4	5	6	7
22	Irregular Heartbeat	0	1	2	3	4	5	6	7
23	Stomach Cramps	0	1	2	3	4	5	6	7
24	Muscle Cramps	0	1	2	3	4	5	6	7
25	Trembling / Tremor	0	1	2	3	4	5	6	7
26	Disturbed Vision	0	1	2	3	4	5	6	7
27	Light Headed	0	1	2	3	4	5	6	7
28	Short of Breath	0	1	2	3	4	5	6	7
29	Joint Pain	0	1	2	3	4	5	6	7
30	Increased Urination	0	1	2	3	4	5	6	7
31	Difficulty Urinating	0	1	2	3	4	5	6	7
32	Stiff Joints	0	1	2	3	4	5	6	7
33	Difficulty Breathing	0	1	2	3	4	5	6	7
34	Excessive Thirst	0	1	2	3	4	5	6	7
35	Fever	0	1	2	3	4	5	6	7
36	Rigid Neck	0	1	2	3	4	5	6	7
37	Loss of Appetite	0	1	2	3	4	5	6	7

38	Nasal Congestion	0	1	2	3	4	5	6	7
39	Sore Throat	0	1	2	3	4	5	6	7
40	Wheezing	0	1	2	3	4	5	6	7
41	Nasal Bleeding	0	1	2	3	4	5	6	7
42	Involuntary Movements	0	1	2	3	4	5	6	7
43	Loss of Memory	0	1	2	3	4	5	6	7
44	Irritability	0	1	2	3	4	5	6	7
45	Uncoordinated Movements	0	1	2	3	4	5	6	7
46	Loss of Consciousness	0	1	2	3	4	5	6	7
47	Abnormal Urine	0	1	2	3	4	5	6	7
48	Insomnia (Sleeplessness)	0	1	2	3	4	5	6	7
49	Vomiting	0	1	2	3	4	5	6	7
50	Itching Teeth	0	1	2	3	4	5	6	7
51	Abdominal Pain	0	1	2	3	4	5	6	7
52	Migraine	0	1	2	3	4	5	6	7
53	General Pain	0	1	2	3	4	5	6	7
54	Constipation	0	1	2	3	4	5	6	7
55	Increased Appetite	0	1	2	3	4	5	6	7
56	Increased Cough	0	1	2	3	4	5	6	7
57	Hallucinations	0	1	2	3	4	5	6	7
58	Increased Flatulence	0	1	2	3	4	5	6	7
59	Ear Pain	0	1	2	3	4	5	6	7
60	Eye Pain	0	1	2	3	4	5	6	7
61	Disturbed Taste	0	1	2	3	4	5	6	7
62	Bruising	0	1	2	3	4	5	6	7

If you are experiencing a symptom not listed above please use the space provided below to describe the symptom(s).

Symptom	Slight			Moderate			Severe
	1	2	3	4	5	6	7
	1	2	3	4	5	6	7
	1	2	3	4	5	6	7

For each symptom marked YES, do you think the symptom was caused by the drug?

Symptom Number	YES	NO	If NO, what is the likely cause?

To what extent would the symptom(s) marked YES prevent you from performing normal day-to-day activities?

Impairment	Symptom Number	Symptom Number	Symptom Number	Symptom Number
Severe				
Major				
Moderate				
Slight				
None				

Place an "X" next to the treatment you think you were given?

- Modafinil: _____ low dose? _____ high dose?
- Placebo: _____